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Assessment of the Correlation Between α-Synuclein and Retinol-Binding Protein 4 with some Biochemical Parameters in Iraqi Parkinson's disease patients

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Abstract

Background: Parkinson's disease is an age-related disease and is very common, ranking second only to Alzheimer's disease. It can be characterized by motor and non-motor symptoms that negatively affect the patient's daily functions to varying degrees. The purpose of this research was to investigate the possible relationship between α-synuclein and Retinol-Binding Protein 4 with some biochemical parameters in Iraqi patients suffering from PD.

Methodology: Fifty patients with PD who attended Al-Ramadi Teaching Hospital as well as 30 full-matched healthy subjects were recruited. Then the concentrations of serum α-synuclein, RBP-4 and other biochemical index (including total protein, albumin, globulin, fasting serum glucose and uric acid) were tested using enzyme-linked immunosorbent assay (ELIZA), spectrophotometric methods as well as calculation.

Results: The results showed a significant increase in serum alpha-synuclein and RBP-4 levels in patients with Parkinson's disease compared to the control group ($P < 0.001$). Significant increases were also observed in total protein, albumin, fasting glucose, and uric acid levels ($P< 0.05$), while globulin levels decreased only slightly ($P=0.1415$). A strong positive correlation was observed between alpha-synuclein and RBP-4. Receptor operating characteristic (ROC) curve analysis demonstrated the high diagnostic value of these biomarkers, with alpha-synuclein achieving an area under the curve (AUC) of 0.944 (sensitivity, 86.0%; specificity, 86.7%). In contrast, RBP-4 achieved perfect discrimination (AUC = 1.000, sensitivity = 100%, specificity = 100%).

Conclusion: The present findings show an association between serum alpha-synuclein proteins and serum RBP4, such that they may be further developed as a reliable biomarker for early and proper PD diagnosis. This will yield novel comprehension of the pathophysiological role of inflammation during this disease onset.

تقييم العلاقة بين بروتين ألفا-سينوكلين وبروتين ربط الريتينول 4 مع بعض المؤشرات البيوكيميائية لدى مرضى باركنسون العراقيين

محمد حسن الشجيري، خالد فاروق الراوي، عرفات حسين الدجيلي

الخلاصة

المقدمة والهدف: مرض باركنسون هو مرض مرتبط بالتقدم في السن ويعد من الامراض الشائعة جدا حيث يحتل المرتبة الثانية بعد مرض الزهايمر ويمكن تمييزه بأعراض حركيه وغير حركيه تؤثر سلبا وبدرجات متفاوتة على وظائف المريض اليومية. أُجريت هذه الدراسة لاستكشاف العلاقة المحتملة بين بروتين ألفا–سينوكلين وبروتين ربط الريتينول 4 (RBP-4) مع بعض المؤشرات الكيميائية الحيوية لدى مرضى باركنسون العراقيين.

العينات وطرق العمل: شملت الدراسة 50 مريضًا تم تشخيص إصابتهم بمرض باركنسون من مستشفى الرمادي التعليمي، بالإضافة إلى 30 شخصًا سليمًا من نفس الفئة العمرية كمجموعة ضابطة. تم قياس مستويات بروتين ألفا–سينوكلين وRBP-4 في مصل الدم باستخدام مقايسة الامتصاص المناعي المرتبط بالإنزيم (ELISA)، بينما تم تحديد المؤشرات الكيميائية الحيوية الأخرى – بما في ذلك البروتين الكلي، والألبومين، والغلوبولين، وسكر الدم الصائم، وحمض اليوريك – باستخدام طرق قياس الطيف الضوئي، مع حساب نسب الألبومين إلى الغلوبولين.

النتائج: أظهرت النتائج ارتفاعًا ملحوظًا في مستويات بروتين ألفا–سينوكلين وبروتين RBP-4 في مصل مرضى باركنسون مقارنةً بمجموعة الاصحاء ($P < 0.001$). كما لوحظ ارتفاع ملحوظ في مستويات البروتين الكلي، والألبومين، وسكر الدم الصائم، وحمض اليوريك ($P < 0.05$)، بينما انخفض مستوى الغلوبولين انخفاضًا غير دال إحصائيًا ($P = 0.1415$). ولوحظ وجود ارتباط إيجابي قوي بين بروتين ألفا–سينوكلين وبروتين RBP-4. وأظهر تحليل منحنى خصائص التشغيل (ROC) القيمة التشخيصية العالية لهذه المؤشرات الحيوية، حيث حقق بروتين ألفا–سينوكلين مساحة تحت المنحنى (AUC) قدرها 0.944 (الحساسية = 86.0%، النوعية = 86.7%)، بينما حقق بروتين RBP-4 تمييزًا مثاليًا (AUC = 1.000، الحساسية = 100%، النوعية = 100%).

الاستنتاج: تشير هذه النتائج إلى أن RBP-4 في المصل و α-synuclein مترابطان وقد يكونان بمثابة مؤشرات حيوية موثوقة للكشف المبكر عن مرض باركنسون ومراقبته، مما يوفر رؤى جديدة حول الدور الفيزيولوجي المرضي للالتهاب في تطوره.

1. Introduction

Parkinson disease (PD) is a complex neurodegenerative disorder characterized by the progressive loss of dopamine-producing neurons in the substantia nigra (SN) (Mollenhauer and von Arnim, 2022). As a result, these neurons in the brain begin to malfunction, leading to dopamine deficiency, which manifests as the accumulation of alpha-synuclein (α-syn) protein in cells, forming structures known as Lewy bodies (LB) and Lewy neuritis (Saini *et al.*, 2024). Various factors, including age-related changes, genetics, oxidative stress, and exposure to pollutants, have been shown to contribute to the etiology of PD (Schapira and Jenner, 2011). Furthermore, diverse genetic and environmental factors vary from person to another one. For example, genetic predisposition may modify environmental effects (Uwishema *et al.*, 2022). α-syn is a protein that consists of 140 amino acids and is found in the presynaptic terminals throughout the brain, which plays a role in controlling the movement of the presynaptic vesicles and their fusion with the synaptic membranes (Nordengen and Morland, 2024). It regulates the synthesis and storage of dopamine (DA) (Henriques *et al.*, 2022). In Lewy pathology, the accumulation of α-syn is a normal and protective response to various biological stressors, including infectious or toxic exposures. The longer the accumulation process lasts, the less of the normal protein remains (Espay and Lees, 2024). α-syn pathology is a prominent feature of PD, and the manifestation of pathogenic variants in the SNCA gene or multiplication of its locus supports a potential causative role of αSyn in PD patients (Kumar *et al.*, 2022). For more than twenty-five years, since the main role of α-syn protein in PD, this finding remained a landmark in research, particularly with the identification of the genetic variants of the disease. Abnormal assemblages of α-syn protein, along with LB, glial cell clusters, and Lewy neural appendages, have been implicated in several sporadic neurodegenerative diseases known as α-syn disorders, including idiopathic PD. Lewy body-associated dementia, pure autonomic failure, Multiple systems atrophy, and Rapid eye movement (REM) sleep behavior disorder. (Calabresi *et al.*, 2023). Mitochondrial dysfunction is one of the pathophysiological causes, as are lysosomal dysfunction, endoplasmic reticulum stress, and α-syn protein aggregation. The accumulation of α-syn protein in the form of aggregates with high molecular weight leads to cytotoxicity and, in turn, may be one of the key contributing factors in the pathogenesis of PD (Henriques *et al.*, 2022). This cellular toxic burden resulting from the accumulation of α-syn may arise from overexpression of the protein or a defect in normal protein removal mechanisms, such as lysosomal autophagy and gene proliferation (Alegre-Abarrategui *et al.*, 2019). Retinol-binding protein 4 (RBP-4) is a lipocalin family with a molecular weight of 21 kDa. is an adipokine primarily secreted by the liver and adipose tissue, employed as the main transport protein for vitamin A (retinol) in the bloodstream. Beyond its classical role in retinol homeostasis, RBP-4 has emerged as a key regulator in metabolic and inflammatory pathways. Elevated serum levels of RBP-4 have been consistently associated with type 2 diabetes mellitus, insulin resistance, obesity, and cardiovascular diseases, largely due to its role in disrupting glucose metabolism and promoting low-grade systemic inflammation (Hussein and Yahya Hammo, 2024); Fan & Hu, 2024). In the setting of neurodegeneration, it has been proposed that RBP-4 may affect neuroinflammation by interacting with retinoid signaling pathways and these are essential in regulating neuronal survival, differentiation and synaptic plasticity. The role of vitamin A deficiency and deranged retinoid signaling in PD pathophysiology has been proposed, as they could enhance dopaminergic vulnerability via oxidative stress and mitochondrial dysfunction (Christou et al., 2012; (Kung *et al.*, 2021). Furthermore, RBP-4 is believed to affect brain insulin signaling, which has been linked to neurodegenerative processes including those observed in PD (Craft, 2005). Therefore, investigating serum RBP-4 levels in PD patients may provide novel insights into the metabolic-inflammatory mechanisms contributing to disease progression and assistance in identifying potential biomarkers or therapeutic aims. Adipokines are biologically active molecules secreted mainly from adipose tissue, and it have important effects in many physiological process, including inflammation (He *et al.*, 2023). Its

primary and sole function is to transport vitamin A (VA), which in turn regulates retinol levels in the blood. RBP4 is primarily synthesized and secreted in the liver and adipose tissue. This adipokine plays a vital role in vision and growth, as well as in metabolic disorders. RBP4 typically binds to transthyretin in a 1:1 ratio in the bloodstream to prevent its filtration by the renal glomeruli (Hu *et al.*, 2023). A previous study indicated that impaired glucose and lipid metabolism, as well as dysfunction of adipose tissue, are associated with the combination of elevated plasma levels of RBP4, an adipokine, and the retinol transporter, which increases the risk of both conventional cardiovascular risk factors, such as blood pressure, and unconventional factors, including cytokines (Zhao *et al.*, 2019). Previous studies have demonstrated that RBP4 is exceedingly associated with obesity in diabetic patients, insulin resistance (IR), renal dysfunction, and various cardiometabolic indices. It has also been reported that RBP4 modulates insulin sensitivity by affecting the expression of the insulin-responsive glucose transporter type 4 (GLUT4) in adipocytes. In addition, α-carotene and β-carotene—dietary precursors of vitamin A—have been linked to Parkinson's disease (PD), with low blood levels or reduced intake of β-carotene being associated with increased risk or progression of PD (Cao *et al.*, 2024; Li *et al.*, 2024; Su *et al.*, 2024). While many local studies have focused on inflammatory biomarkers in various pathological conditions, the present study is distinct in its evaluation of RBP4 and α-syn, along with their correlation with selected biochemical parameters in PD patients (Alaaraji, 2019; Fayez, Rashied and Al-Alaaraji, 2020; Al-Rawi *et al.*, 2022). The primary objective of this study is to investigate the relationship between RBP4 and α-synuclein, their inter-correlation, and their association with disease severity in Parkinson's disease.

2. Materials and Methods

This study included 50 patients diagnosed with Parkinson's disease (PD) and 30 healthy controls (HCs), all recruited from individuals attending Ramadi Teaching Hospital in Iraq between March 2023 and November 2024. Participants were randomly selected and ranged in age from 50 to 70 years.

2.1. Rejection principles for PD Patients

After full clinical examination by the consultant physicians, patients were free of severe diseases or infection at time of study and with known illness, while the patients suffered from any chronic disease were excluded.

2.2. Rejection principles for HCs

The rejection principles were chosen among those who were healthy controls with respect to non-diabetic, no other endocrine disorders, non-hypertensive, or kidney diseases, and they were free from acute illnesses and infections at the time of sampling. This study was approved by the ethics committee of Anbar university, and our inquiry was conducted in correspondence with the standards of the Declaration of Helsinki (1964).

2.3 Measurement of Biochemical Parameters

Samples of blood were taken after fasting for 8-12 hours, about five mL of venous blood were drawn from all subjects (control and patients), blood was collected in a gel plain tube, for obtaining serum through centrifugation after clotting within room temp. (18–25 °C) at 1500 xg for 15 min. Serum that obtained was divided for two groups. First one was utilized for biochemical parameters, which FSG was determined for each sample by a glucose oxidase method (Randox Company, U.K.), uric acid, total protein, albumin and globulin levels were measured by colorimetric enzymatic method (LINER Chemicals/ Spain). Second one of the sera was stored at -20 °C to measure serum α-synuclein and RBP-4 using an enzyme linked immune sorbent assay (ELISA) kit from Bioassay Technology Laboratory Company, China.

2.3. Statistics Analysis

Statistical investigates of our results were done by GraphPad Prism 8.02 provided from (GraphPad Software, La Jolla, CA, USA). The consequences are stated as mean and standard deviation (SD). The statistical importance of the differences among the subjects with and without PD was verified by independent samples t test, bivariate associations were tested through a Pearson correlation investigates with two-tailed, while the precision of the investigation was measured through Area under the curve (AUC) of the Receiver Operating Characteristic (ROC), sensitivity (Sen%), specificity (Spec%) and likelihood ratio (LHR), as well cut-off value were calculated for each variable. $P\text{-}value \leq 0.05$ was measured to be statistically important.

3. Results

The means and SD of the main outcomes between patients and healthy groups are shown in Table1. The results showed that there were no significant differences in age and body mass index (BMI), we took matching BMI and age to come up with perfect results, diastolic blood pressure (DBP), systolic blood pressure (SBP), and mean arterial pressure (MAP), with p values > 0.05, as indicated in Table1.

Table1: Mean and SD for some Variables in Healthy Controls and PD Patients

Parameter	Healthy controls	Patients	
	Mean ±SD	Mean ±SD	P value
Age Year	60.63±4.514	63.34±8.366	0.1066
BMI kg/m2	23.99±1.326	23.27±1.541	0.0857
SBP mmHg	122.2±2.230	121.8±6.270	0.7471
DBP mmHg	81.00±1.259	79.10±7.454	0.1712
MAP mmHg	94.72±1.328	93.33±6.596	0.2569

Table2, Fig.1 and Fig.2 show the standard experimental features of the subjects are described, α-synuclein concentrations were significantly elevated in patients (0.2285 ± 0.0281 pg/mL) relative to healthy (0.1832 ± 0.0088 pg/mL). Similarly, RBP-4 level was markedly higher in patients (0.0739 ± 0.0059 ng/mL) than in healthy (0.0524 ± 0.0038 ng/mL. Total protein, albumin and uric acid levels were significantly reduced in patients in comparison to healthy respectively. FSG was significantly higher in patients compared to healthy.

Table2: Mean and SD for Some Variables in Healthy Controls and PD Patients

Parameter	Healthy controls	Patients	
	Mean ±SD	Mean ±SD	p-value
FSG mg/dL	82.00±9.469	91.00±11.08	0.004
T. Proteins g/dL	6.783±0.3621	6.482±0.7159	0.0352
Albumin g/dL	4.380±0.2188	3.872±0.2865	<0.001
Globulins g/dL	2.403±0.3146	2.610±0.7206	0.415
Uric acid mg/dL	5.197±0.3792	3.918±0.5535	<0.001
α-synuclein pg/mL	0.1832±0.0088	0.2285±0.0281	<0.001
RBP-4 ng/mL	0.0524±0.0038	0.0739±0.0059	<0.001

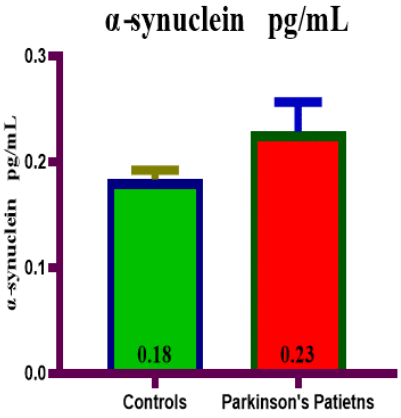

Figure1: Mean ± SD for α-synuclein in Control and Parkinson Patients

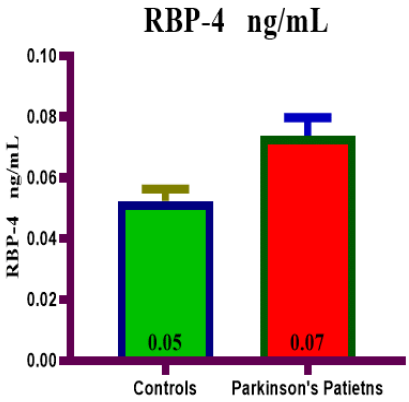

Figure2: Mean ± SD for RBP-4 in Control and Parkinson Patients

Table3 has shown Important positive correlation was detected among α-Synuclein with RBP4 (r=0.557, P<0.001), while negative relationship between α-Synuclein with Albumin and Uric Acid (r=-0.42, P<0.001) and (r=-0.503, P<0.001), respectively.

Table3: The Correlation of Alpha-Synuclein With Studied Variables

Parameter	r (Alpha-Synuclein pg/mL)	p-value
Alpha-Synuclein pg/mL	1.000	0.000
RBP-4, ng/mL	0.557	<0.001
Age, Years	0.187	0.096
BMI, kg/m^2	-0.028	0.803
SBP, mmHg	-0.160	0.156
DBP, mmHg	-0.191	0.089
MAP, mmHg	-0.196	0.082
F.S.G, mg/dL	0.312	0.005
T. Protein, g/dL	-0.196	0.082
Albumin, g/dL	-0.427	<0.001
Globulins, g/dL	0.053	0.642
Uric Acid, mg/dL	-0.503	<0.001

Table4 shows very Important negative correlations were detected among RBP4 with albumin and uric acid (r=-0.605, P<0.001) and (r=-0.745, P<0.001) respectively.

Table4: The Correlation of RBP-4 With Studied Variables

Parameter	r (RBP-4 ng/mL)	p-value
RBP-4, ng/mL	1.000	0.000
Alpha-Synuclein pg/mL	0.557	<0.001
Age, Years	0.127	0.260
BMI, kg/m^2	-0.309	0.005
SBP, mmHg	-0.020	0.858
DBP, mmHg	-0.116	0.308
MAP, mmHg	-0.094	0.409
F.S.G, mg/dL	0.284	0.011
T. Protein, g/dL	-0.129	0.253
Albumin, g/dL	-0.605	<0.001
Globulins, g/dL	0.227	0.043
Uric Acid, mg/dL	-0.745	<0.001

Table5 has shown ROC curve checking offered that the best biomarkers were fit to distinguish patients with PD from HCs. The ROC curve shows up that the α-Syn and RBP4 levels have exhibited an excellent method to distinguish' between healthy group each on individuals and patients with PD [AUC = 0.9440; Sensitivity 86%; Specificity 86.67%] and [AUC = 1.000; Sensitivity 100%; Specificity 100%], for α-Synuclein and RBP4, respectively (Figs.3 and Fig.4 respectively). For this, it can be said that α-Synuclein and RBP4 are definitely functions for diagnosing PD.

Table5: Area Under the ROC Curve For A-Synuclein and RBP-4

Parameter	AUC	Positive if COV	Sensitivity٪	Specificity٪	Likelihood Ratio
α-synuclein, pg/mL	0.9440	> 0.195	86.00	86.67	6.450
RBP-4, ng/mL	1.000	> 0.060	100.0	100.0	

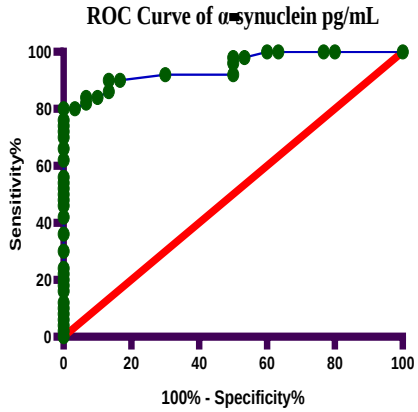

Figure3: AUC of ROC for α-synuclein in PD Patients

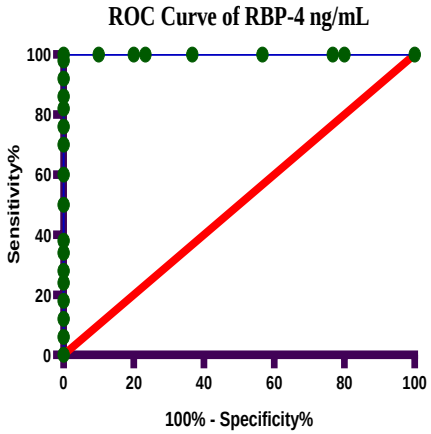

Figure4: AUC of ROC For RBP-4 in PD Patients

4. Discussion

Parkinson's disease is thought to be influenced by a combination of genetic and environmental factors(Periñán *et al.*, 2022). PD is clinically distinguished by changes in motor function, In particular, tremor, rigidity, bradykinesia, and postural instability. These symptoms are often referred to as the cardinal features of Parkinson's disease. Non-motor manifestations include loss of smell, cognitive decline, personality changes, depression, anxiety, fatigue, autonomic dysfunction symptoms, and others, are observed in the disease because of pathophysiological alterations(Munhoz *et al.*, 2024). The detection of physiopathology has greatly contributed to the understanding of the clinical features. According to Uwishema et al. (2022), a decrease in the quantity of dopamine neurons in the substantia nigra has been observed, accompanied by the presence of Lewy bodies in the remaining neurons(Angelini, Paparella and Bologna, 2024). The result of this study detected a higher level of total α-Syn in serum of PD patients than HCs, elevated serum concentrations of α-Syn in patients with PD could indicate disease-linked neuronal damage that leads to an elevation of extracellular α-Syn in the brain and subsequent leakage to the periphery. Alternatively, higher amount of total α-Syn in plasma could correspond to differences in the conformation properties of α-Syn in the patients compared to the HCs (Shu, Zhang and Gu, 2024). Several studies with ELISA showed serum levels of α-Syn in patients with PD were higher than in HCs(Lee *et al.*, 2006) (Duran *et al.*, 2010), Two other studies that measured plasma α-Syn via ELISA and mass spectrometry (Foulds *et al.*, 2011); Park et al., 2011) found similar levels in both PD patients and controls. In larger cohorts that assessed levels of total a-Syn in plasma via Luminex assays, no difference was found between PD patients and controls (Mata *et al.*, 2010). However, several other studies found decreased alpha-synuclein levels in the plasma of PD patients compared to controls, and there was no

significant difference in this parameter between the two groups (Chang *et al.*, 2020) Thus, although peripheral alpha-synuclein (serum or plasma) is considered a promising candidate biomarker, the present study results are inconsistent. It is due to several things that are difficult to avoid, such as the various stages of disease and duration of illness of PD patients included in the study. In addition, most studies are still in the cross-sectional method, and the control group included in the study is almost always normal subjects (Syafrita and Susanti, 2022). There is a heightened interest in the most severe stages of Parkinson's disease. Some studies identified considerable disabilities, but also recognized remaining treatment options . Adjusting levodopa can alleviate some symptoms in advanced Parkinson's disease, albeit at the risk of worsening dyskinesias or psychosis. (Brys *et al.*, 2019). One of the possible pathogenic causes that were not hypothesized before is that PD is associated with retinoid depletion within the brain tissue. This hypothesis is based on the presence of diffuse stellate cells system and that stellate cells exist mainly in the liver as well as in extrahepatic sites including the kidney, colon, pancreas, lung, and heart (Panebianco *et al.*, 2017). As a response to tissue injury, these stellate cells become activated myofibroblasts that lose their V_A storage capacity, and this is the fundamental explanation for hepatic fibrosis pathogenesis (Zhao and Burt, 2007). Within the brain, astrocytes mimic HSCs both structurally and functionally. Further, in response to brain injury, astrocytes become activated in many brains pathological conditions including PD, just like HSCs (Joe *et al.*, 2018). Thus, if PD is associated with V_A deficiency within the brain tissue, V_A supplementation would selectively target the V_A-deficient brain. Epidemiological and clinical studies investigating the link between V_A or retinoids/carotenoids and PD have not shown a clear effect. Original studies, meta-analyses and reviews have mainly found an absence of link between the disease and the dietary intake (Ciulla *et al.*, 2019); Boulos et al., 2019). Previous studies found an association between low dietary intake of β-carotene or low levels of blood α-carotene, β-carotene and lycopene with the progression of PD (Yang et al., 2017; Kim et al., 2017). These studies are based on nutritional intake or retinol blood levels, and therefore they do not provide information about the vitamin A status of patients, i.e., the bioavailability of vitamin A and retinoic acid (RA) for target organs, such as the brain. The level of retinol in the blood is correlated to nutritional intake, but is also tightly controlled by homeostatic processes to maintain a constant value around 2 µg/ml (Féart *et al.*, 2010). Thus, the retinol level in the blood is not a reliable marker of vitamin A and RA functionality. More relevant measures would be gene expression of RA receptors (RAR/RXR) or retinol level in the cerebral spinal fluid (Royal, Gartner and Gajewski, 2002). Measuring RA concentration in the blood or the cerebral spinal fluid would also be more informative, but it is highly challenging due to its biochemical instability (Kane and Napoli, 2010). Despite α-synuclein and RBP-4 were increased significantly, but the increase in the concentration of α-synuclein was more than the other with bigger AUC and more sensitivity and specificity making this protein the most relative biomarker to PD. Due to the limitations of the present study, large longitudinal studies with standardized assays for serum α-Syn and RBP-4 are required to ratify the value of serum α-Syn and RBP-4 as biomarkers for PD.

Conclusions

Current study showed that α-synuclein concentration was related with Retinol binding protein-4 positively, while it associated with Albumin and Uric Acid negatively, also it was showed negative Correlation between RBP-4 with Albumin and Uric Acid which means we can use these variables as indicators of PD. This study has thus shed new light on the complex interplay between inflammation and PD. Current data was shown that higher concentrations of α-synuclein and RBP-4 is associated with the development of PD, and those findings explain the significance of these biomarkers and its implications for the pathophysiology of PD. Both α-synuclein and RBP-4 are part of PD's pathogenesis, and they may be used as possible biomarkers and predicator of PD.

Author Contributions

M.H. Alshujairi designed the study and supervised the overall research project. K.F. AL-Rawi conducted the experiments, composed the data, and contributed to the methodology section. A.H. Al-Dujaili performed the data analysis, statistical evaluation, and wrote the initial draft of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no relevant financial or non-financial interests.

Ethical Approval and Consent

Ethical approval for the present study was granted by the Ethical Approval Committee of the University of Anbar, College of Science.

Approval was obtained under Reference No. 298 (26/12/2024), valid from 15/08/2024.

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