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ORIGINAL ARTICLE

The relationship between Adiponectin and Serum Oxidative Stress factors in Parkinson's Disease

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Abstract

Background: Parkinson's disease [PD] is a common neurodegenerative disease. Oxidatant stress factors are a main cause in the pathogenesis of PD.

Our study aimed to estimate the relations between serum levels of vitamin C, ferritin, transferrin, Nitrite Oxide [NOx] and Adiponectin in correlation with parkinsonian severity.

Methods: a case control study done on27 PD patients and 27 healthy subjects, measuring serum vitamin C, ferritin, transferrin, Nitrite Oxide [NOx] and Adiponectin levels with UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS) was done to detect parkinsonian severity in the patients.

Results: there is a significant difference between the two studied groups regarding age, NOx, vitamin C, and ferritin level. There is also significant difference between the patients and control groups regarding Adiponectin level [it is significantly higher among case group].

The cutoff point of serum Adiponectin in diagnosis of Parkinsonism is ≥12.115 μg/mL and the area under curve was 0.866, sensitivity 92.6%, specificity 81.5%, the value of positive prediction was 83.3%, negative predictive was 91.7% and overall accurateness was 87%.there were a positive correlation between Adiponectin and NOx, UPDRS and ferritin among case group.

Conclusion: Serum levels of vit C, ferritin ,NOx and Adiponectin are significantly higher in patients with PD. In addition, it can be suggested that to have a role in progression of PD. More researches are needed on more patients and different ethnics to afford more data about the disease severity and the outcome.

INTRODUCTION

Parkinson's Disease (PD) is one of the commonest neurodegenerative disease. That caused by degeneration of dopamine-producing neurons at the substantia nigra, and by time the progression of the disease increase with more degenerations of these cells [1].

PD presented by bradykinesia, rigidity, tremor, and walk disturbance. Beside non-motor manifestation of PD including depression, anxiety, swallowing difficulty and sphincter disturbance [2].Adiponectin level are associated with people with variant degrees of obesity, dyslipidemia and diabetes mellitus. [3]Many neurodegenerative disorders affected by adiponectin in their pathogenesis,Other study detect that the Adiponectin has several useful roles as anti-inflammatory effect and it also has also a neuroprotective functions.[4]Many trace elements have a vital function in harmonizing oxidative stress inside the human cells. The mechanism by which the construction of free radicals is more than the defense mechanism of useful antioxidant factors which happened inside the human cells as oxidation stress mechanism[5].

Oxidative stress factors are important in initiating and progression of PD manifestations [6].

The mechanism in which the creation of oxidant free radicals is remote with the defense mechanism of antioxidant factors. [7]. The deposition of iron inside the human cells is similar to the formation of

oxidative stress free radicals factors [8]. Transferrin is obviously increased in PD patients compared to healthy one [9].There is an relationship between serum iron and ferritin levels, An increase of iron in the cells leads to increase level of serum ferritin ,so high iron level mimic the synthesis of free radicals, which has a role in the brain tissue degeneration [10]. Nitrite Oxide [NOx] is formed by nitrate oxide synthase enzyme. High NOx level can induce inflammatory reactions mechanism that to cell degeneration. [11]Vitamin C has antioxidant effect and neurotransmitter as dopamine secreting neurons in the brain cells . [12].

Aim of the Work

we aimed to detect if there are association between serum levels of vitamin C, ferritin, transferrin, Nitrite Oxide [NOx] and Adiponectin with disease severity in PD.

PATIENTS AND METHOD

Participants

This study was done in neurology department and neurology outpatient clinic, faculty of medicine, zagazig university hospital on patients with parkinsonian disease , according to the UK Parkinson's Disease Society [13]

Excluding Patients with secondary Parkinsonism, other central nervous system diseases, hepatic, hematologic, neoplastic, inflammatory disorders and patients taking antioxidant drugs.Approval by the Institutional Review Board was obtained prior to conducting the study.[IRBs#456/1-july-2024], matching The Code of Ethics of the World Medical Association [Declaration of Helsinki] .All patients signed full consent before enrollment in our study, our study is a case- control study done on 27parkinsonian patients and 27 healthy control participants ,between January 2023 and June 2024.

Study methodology

On out patients clinic, blood specimens [5 mL] were taken from peripheral vein of participants, and centrifugated at 3000 rpm for 15 min at room temperature for serum isolation , the serum transferred into micro tubes and saved. Measuring serum levels of vitamin C, Nitrite Oxide [NOx] , ferritin, transferrin, and serum adiponectin was done by using ELISA technique using commercial kits by Stat Fax 303plus microstrip reader instrument . In the next step, an axial brain CT and or MRI brain without contrast was performed**.**

Clinical manifestation assessment

Detailed medical history and general and neurological examinations were done to all participants at hospital arrival.

Parkinsonism disease progression severity evaluation

Unified Parkinson's Disease Rating Scale [Updrs] [14]

Laboratory examinations

Serum levels of vitamin C, Nitrite Oxide ,ferritin, transferrin, and serum Adiponectin.

STATISTICAL ANALYSIS

Data analysis was performed using the software SPSS [Statistical Package for the Social Sciences] version 26 . Quantitative variables were described using their means and standard deviations or median and interquartile range according to type of data. To compare quantitative data between two groups, independents sample t test [for normally distributed data] and Mann Whitney test (for not normally distributed data) were used. Spearman correlation coefficient test was used to assess power and path of correlation between two variables. The level significance was $P<0.05$.

RESULTS

Table (1): Comparison between the studied groups regarding baseline and laboratory data

	Case group N=27(%)	Control group N=27(%)	χ^2	p
Gender				
Male	16 (59.3%)	14 (51.9%)	0.3	0.584
Female	11 (40.7%)	13 (48.1%)		

	Case group N=27(%)	**Control group N=27(%)**	χ^2	**p**
Smoking Yes No	 8 (29.6%) 19 (70.4%)	 4 (14.8%) 23 (85.2%)	1.714	0.19
Diabetes Yes No	 12 (44.4%) 15 (55.6%)	 13 (48.1%) 14 (51.9%)	0.074	0.785
Hypertension Yes No	 14 (51.9%) 13 (48.1%)			
	Mean ± SD	**Mean ± SD**	t	p
Age (year)	67.48 ± 6.73	62.11 ± 5.03	3.221	0.002*
UPDRS	3.37 ± 0.74	-	-	-
Nox *µmol/L*	31.26 ± 2.23	16.95 ± 3.58	17.642	<0.001*
Vitamin C mg/dl	18.65 ± 2.14	3.06 ± 1.1	-33.682	<0.001*
Ferritin ng/ml	121.3 ± 6.58	87.4 ± 29.32	5.862	<0.001*
Transferrin mg/dl	256.98 ± 8.65	296.44 ± 40.37	-1.569	0.128

χ^2Chi square test independent sample t test *p<0.05 is statistically significant

Table (2): Comparison between the studied groups regarding serum adiponectin

	Case group n=27	**Control group n=27(%)**	Z	**p**
	Median(IQR)	**Median(IQR)**		
Adiponectin ug/ml	14.13(12.7 – 16.7)	8.34(5.98 – 9.5)	-4.62	<0.001*

Z Mann Whitney test *p<0.05 is statistically significant

Table (3): Performance of Adiponectin in diagnosis of parkinsonism

Cutoff	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**P**
≥12.115	0.866	92.6%	81.5%	83.3%	91.7%	87%	<0.001*

AUC area under curve PPV positive predictive value NPV negative predictive value *p<0.05 is statistically significant

Table (4): Correlation between Adiponectin, UPDRS and the studied parameters among case group

	Adiponectin		UPDRS	
	r	P	R	P
Age (year)	-0.108	0.593	0.186	0.353
Nox	0.576	0.002*	0.643	<0.001**
Vitamin C	-0.643	<0.001**	-0.487	0.01*
Ferritin	0.368	0.006*	0.45	0.016*
Transferrin	-0.063	0.755	0.19	0.343
UPDRS	0.864	<0.001**	-	-

r Spearman rank correlation coefficient *p<0.05 is statistically significant

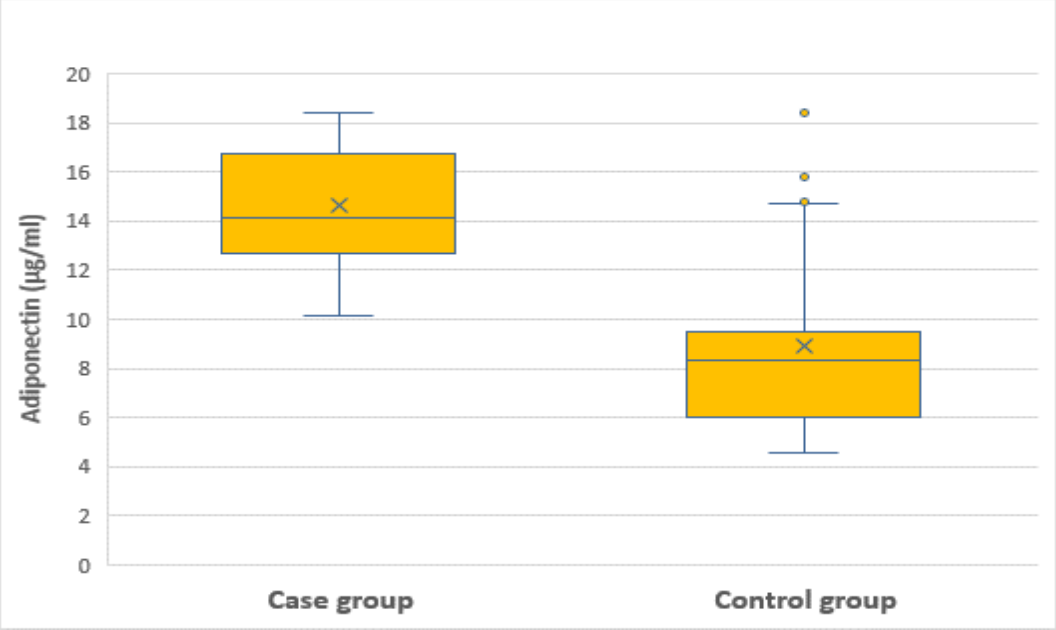

Figure (1) Boxplot showing comparison between groups regarding serum adiponectin

DISCUSSION

Oxidative stress factors have a vital role in the pathogenesis of initiating and progression of parkinsonian disease manifestations, by this mechanism the production of harmful free radicals is more potent than the defense action of antioxidant ,which leads to cellular degeneration by oxidative stress pathogenesis[6] . The substantia nigra neurons secreting dopamine in the midbrain nuclei , are more vulnerable to oxidative stress free radicals more than other neurotransmitter neurons due to decrease defense action of the antioxidant factors, like a high serum iron can lead to oxidation of dopamine, this is one of

these mechanisms [15].Adipose tissue is not only a storage tissue, but also act as an endocrine tissue , able of secretion of many factors that can control many physiological function either positively or negatively, one of these factors produced by the adipose tissue is Adiponectin [16] .The metabolic functions of Adiponectin metabolic are mainly on the adipose tissue, liver, and muscle, affecting the metabolism of glucose and free fatty acids [17].In our study we establish that ferritin level had a significant difference between patients and control participants ,and transferrin levels were non significantly lower in our patients .These results were in accordance with [Chen et al.,2023] who establish that ferritin level was higher in their parkinsonian patients but by different method via measurement of ferritin level and transferrin receptors TfR in neuronal derived exosomes ,they attributed that raise of ferritin level in neural-derived exosomes in the plasma related to increase neuronal iron deposition in PD and this could explain also our lower level of transferrin ,Ferritin could be also removed throughout the exosomal pathway, and serum iron level can reflect serum level of ferritin.[18]. Ferritin has a complex regulatory pathway by cellular iron levels through the iron protein system regulation ,as soon as the iron concentration level overcome the capability of the transferrin transport saturation , the overloaded iron starts a redox route metabolic action that creates hydroxyl free radicals[18,19].Also our results were in association with [Wei et al.,2018] in their meta-analysis they found higher serum level of ferritin among patients group but similar levels of transferrin ,this may be due to different number of individuals involved in both studies.[20]. On the other hand we were in the contrary of (Jiménez-Jiménez et al.,2021) in their meta-analysis as they found lower serum ferritin levels but also similar transferrin levels.[21]. Regarding vitamin C level in our study we observed that vitamin C level was significantly lower in patients group and NOx level was significantly higher in patients group also ,this was in concurrence with (Barmaki et al.,2021 and Ide et al., 2015) who detected the higher level of NOx and lower level of Vitamin C level in their patients ,and they explained that by the role of vitamin C as antioxidant as it protects neurons from glutamatergic neurotoxicity, oxidative stress is an essential cause in initiating and increase PD progression.[12,15]. The mechanism by which the creation of oxidatant free radicals is more potent than the defense mechanism of antioxidant system is happened intracellular as a harmful stress oxidative free radicals [7]. The higher level of NOx in our patients group that was in accordance with (Barmaki et al.,2021, Kouti et al.,2103) who found higher levels of NOx in the serum and peroxynitrite in patients with parkinsonism and it was positively correlated to UPDRS .[2,15]. In another study done by (Lian et al., 2024) they found that serum NOx was lower in parkinsonism patients with anxiety than those without anxiety and the high NOx level can aggravate anxiety symptoms in patients with mood disorders ,this difference may be due to different selection of patients as they compared the level of NOx between parkinsonian patients and did not compare with healthy individuals as they stated that they were focusing on parkinsonism and anxiety[22]. Adipose tissue is act as an endocrine organ, able to secret multiple factors that can affect many physiological function either positively or negatively [17]. It has an inflammatory and immune modulatory functions , through production of cytokines and enhance immune cells proliferation [23]. In our study we detect that the serum level of adiponectin was high significance in patients group than controls, our findings were in accordance with (Katoaka and Sugie ,2020) ,they found higher serum adiponectin level in their participants ,They attributed this to the role of adiponectin in modulating pro-inflammatory process and encourage the secretion of interleukin (IL-6)in human astrocytes and the composition of lipid rafts [24]. In this study, we establish that there were a significant positive relationship between Adiponectin level , NOx ,ferritin and vit C with

parkinsonian severity using UPDRS with agreement with study done by [25,26].

CONCLUSION

ferritin, NOx, and Adiponectin serum levels in PD patients were higher than normal healthy control participants. However vit c serum level was high in comparison to PD patients. As well as vitamin C deficiency and high serum ferritin ,NOx and Adiponectin can be utilized as a biomarker for parkinsonian disease evaluating development and severity . And so oxidative stress factors have a role in the pathogenesis of cells producing dopamine degeneration.

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