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Role of Homocysteine and water-soluble vitamins in Parkinson's disease: A case-control study in Iraq

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Abstracts

Parkinson's-disease (PD) is a neurological incident that becomes exacerbated with age. The research aims to investigate the role of Homocysteine, Vitamin B12, folic_acid, and other micronutrients in PD, focusing on how elevated homocysteine levels and deficiencies in these nutrients may contribute to neurodegeneration, and exploring their role in potentially intensifying disease progression and deteriorates patient outcomes.

A case-control study was conducted to examine various blood biomarkers in 200 participants grouped as 100 control and 100 PD patients (59% were female and 41% male), ages ranging from 43-67 years. About 52% of patients and 43% of the control group were smokers. Samples of venous blood were collected from each individual to measure levels of water-soluble vitamins (Vit B12 and folic acids), different types of micronutrients including iron, magnesium (Mg), phosphorus (Ph), and zinc (Zn), in addition to the measurement of Homocysteine level and glutathione. A highly significant_ decrease ($P<0.01$) in all the measured biochemical parameters, except Mg, folic acid, and Homocysteine were significantly elevated in the patients' group compared to the control group. The results of the study conclude very highly significant sensitivity and specificity of Mg, folic acid, and Homocysteine in PD patients that confirm the significant role of those biochemical markers in the disease.

Keywords: Parkinson's disease, Homocysteine, Folic acid, Vitamin B12, Micronutrients, Glutathione.

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1. Introduction:

The frequency of Parkinson's disease (PD), the subsequent most prevalent neurological illness after Alzheimer's disease, progressively rose related to age and primarily affected the elderly. PD is a mobility condition that impacts people's everyday lives in a significant way (1). PD results in the progression of both motor and non-motor symptoms. As people age, the risk and extent of PD rise, with about a 2:1 male-to-female ratio (2). The prodromal phase of PD is a discernible stage that precedes the clinical diagnosis (3).

PD is a multisystem neurologic condition, although the motor symptom of Parkinsonism, which is caused by a malfunction of dopaminergic neurons, is still the mainstay of diagnosis. Sleep issues, cognitive decline, mood and attitude changes, autonomic dysfunction (constipation, urogenital diseases, and orthostatic hypotension), and sensory symptoms (pain and hyposmia) are examples of non-motor symptoms. The beginning of motor symptoms may be prodromal because nonmotor symptoms, especially hyposmia and rapid-eye-movement (R.E.M.) sleep_ behavior disorder, which is distinguished by limb movements that mimic

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running or flailing and absence of normal atony during REM sleep, frequently occur years before the onset of motor symptoms (2,4-5).

Cognitive decline and cardio-cerebrovascular accidents have been linked to elevated levels of circulating Homocysteine (Hcy). When levodopa is used to treat PD, catechol-O-methyltransferase (COMT) metabolizes the drug, which tends to raise circulating Hcy levels even more. The vitamins B12, B6, and folic acid are co-factors for COMT. Hcy increase is thought to be caused by accumulating deficits of certain vitamins (6). Vitamins that are involved in the metabolism of cytokines, including Vitamin B12 & Vitamin B9, contribute to the standards of neurodegeneration (7). Hyperhomocysteinemia (HHcy) can also be linked to a number of pathological diseases, including diabetes mellitus, hypertension, renal insufficiency, alcohol misuse, a lack of exercise, and old age (8,9).

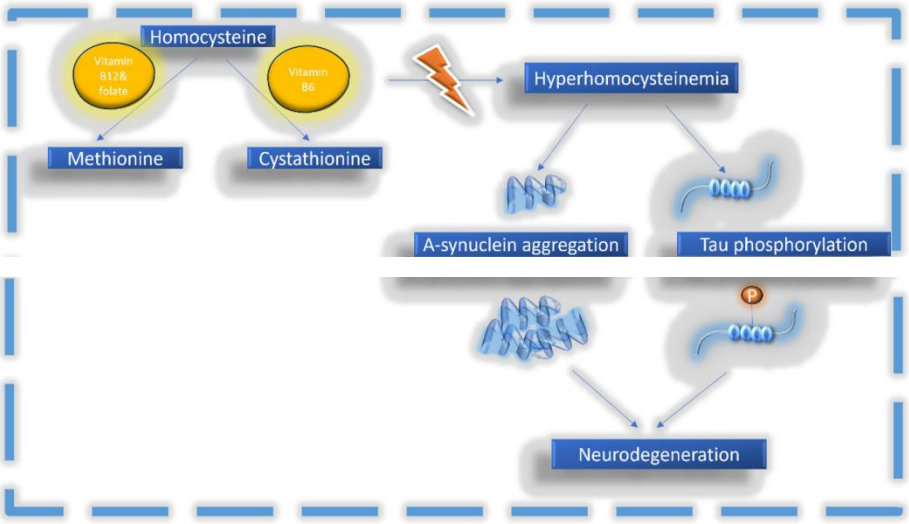


Figure 1. Vitamin cofactors influence Hcy metabolism. HHcy may raise the amounts of phosphorylated tau and promote the abnormal buildup of α-synuclein (10).

The onset and course of Parkinsonian disorders are linked to both Hcy and an imbalance of its vital vitamin cofactors (10).

Multiple reasons, including both hereditary and non-genetic ones, are thought to contribute to Parkinson's disease. About 20 % of people with Parkinson's disease (monogenic Parkinson's disease) have shown genetic variations and significant impact sizes. Variants in LRRK2 (found in about 1 to 2% of all cases and up to 40% of familial cases), GBA1 (found in 5 to 15% of cases and most prevalent in populations with Ashkenazi Jewish or North African ancestry), and VPS35 and SNCA (found in less than 1% of cases) are among the less common variants in autosomal dominant PD with incomplete penetrance. The majority of instances that manifest early in life are caused by recessively inherited PD variations, including PRKN, PINK1, and DJ1. A dose-dependent, 40% or higher risk of PD a part of private or occupational exposure to pesticides (such as paraquat, rotenone, 2,4-dichlorophenoxyacetic acid, and several organochlorines and organophosphates) or chlorinated solvents (such as trichloroethylene and perchloroethylene). These poisons can disrupt mitochondrial function, damage specific dopaminergic neurons, motor dysfunction, and other alterations (8-11).

In the brain, glutathione performs a variety of tasks, primarily serving as a redox regulator and antioxidant. Numerous researchers discovered that people with PD have subclinical vitamin B12 deficiency and reduced amounts of GSH, which are the causes of oxidative stress, which has been implicated in the pathophysiology of the disease, particularly neuronal necrosis; they also hasten the accumulation of untrustworthy proteins (Lewy bodies) and dopaminergic neuron neurodegeneration (12,13).

Vitamin B12's likely antioxidant properties included protecting glutathione and scavenging reactive oxygen species directly and indirectly, respectively, reducing oxidative stress caused by Hcy; reducing oxidative stress brought on by advance_glycation_end (AGE)-products; and adapting cytokine and growth factor invention to promote inflammation (act as a causative agent) and more reactive oxygen species production (14). Furthermore, by altering proteins, lipids, and carbohydrates, reactive oxygen species can destroy useful substances and tissues. Additionally, oxidative stress and cell destruction are linked to dysregulation of iron metabolism (15,16).

Patients with anemia were also shown to have a higher risk of PD than those without anemia. While PD patients' substantia nigra has been found to have inadequate iron, anemia impairs erythropoiesis and increases eryptosis. High dietary iron consumption and elevated blood iron levels lower the risk of PD (16).

One of the main causes of the pathophysiology of sporadic PD may be magnesium insufficiency. By decreasing Ca2+ transport, Mg2+ regulates the activation of the N-methyl-D-aspartate receptor (NMDAR), which is essential for regulating neuronal function. Abnormal NMDAR activity has been linked to the pathogenesis of some neurological and neuropsychiatric conditions. Mg2+ can prevent α-synuclein from aggregating both by itself and in conjunction with Fe2+. Caffeine consumption may result in magnesium insufficiency, since magnesium deficiency lowers one of the environmental protective variables (nicotinism), it is one of the factors that increases the chance of developing PD (17).

The human body uses zinc more than any other trace element. In the brain, Zn2+ functions as a synaptic transmitter. One important contributing component to the development of Parkinson's disease is known to be changes in intracellular zinc homeostasis (18). Blood levels of phosphorus are crucial to the pathophysiology of PD because they may be linked to the degradation of nigrostriatal dopaminergic neurons (19).

The study's goal is to assign a possible pathogenetic role of hypovitaminosis, diminished concentration of certain minerals, and hyperhomocysteinemia which could be of paramount importance for enhancing the precision of PD diagnoses and prognoses and identifying a novel treatment target.

There are a number of gaps and obstacles in the research of PD, including a lack of trustworthy biomarkers for the course of the illness, difficulty in early diagnosis, and limited knowledge of its complicated mechanism.

Key Points of Parkinson's Disease:

Degeneration of neurons and the presence of Lewy bodies in some areas of the nervous system, particularly in dopaminergic brain-stem neurons, are hallmarks of PD, a degenerative ailment that often manifests later. Motor symptoms of PD include asymmetric bradykinesia, stiffness, tremor, and imbalance (20,21).

• Mood, sleep, sensory, cognitive, and autonomic dysfunction are prevalent; they may appear years before motor symptoms (prodromal PD) and worsen during the illness.

• About 20% of cases are caused by gene variations. The majority are caused by toxic and head injuries. Reduced risk by exercise.

• Motor fluctuations can be effectively treated by deep brain stimulation surgery to halt the progression of the disease, as no motor symptoms result in

significant morbidity. It is beneficial to have comprehensive multidisciplinary treatment (20,21).

2. Subjects, Materials and Methods:

2.1. Subjects & Methods:

This study involves (200) case-control participants, 100 as a control group without Parkinson's disease, and 100 diseased patients with Parkinsonism, diagnosed by a specialized physician per the applicable requirements. The ages of subscribers were matched between patients and control groups, ranging from 43 to 67 years old. All patients enrolled in this study were taking L-dopa, a treatment for PD. A percentage of 37% of PD patients have another disease like diabetes mellitus type 2, hypertension, and heart disease, while only 7 individuals from the control group have diabetes mellitus type 2.

It took three months to collect samples for the study. Verbal consent was taken from all engagements before the study commenced.

Exclusion criteria: any other neurodegenerative disorders and other treatments for the central nervous system.

Five ml venous blood sample in a gel tube, coagulated for 10-15 minutes, centrifuged at 3000 RPM at room temperature for 15 minutes. The serum was carefully collected, aliquot, and preserved at -20°C.

2.2. Materials:

For estimation of iron, magnesium, phosphorus, and zinc concentrations use a spectrophotometer apparatus, whereas, for ELISA kits utilize ELISA Human reader and washer apparatus.

Utilize the kits and methods listed below from the specified producers and places of origin.

Tests	Technique	Company	Origin
Human Vitamin B12(VB12)	Sandwich technology - ELISA Kit. Cat.No：YHB3198Hu	SHANGHAI YEHUA Biological Technology	China
Human folic acid (FA)	Sandwich technology -ELISA kit. Catalog No: YHB1228Hu	SHANGHAI YEHUA Biological Technology Co., Ltd.	China
Human Homocysteine (Hcy)	Sandwich-ELISA Kit/ Catalog No: YHB1572Hu	SHANGHAI YEHUA Biological Technology Co., Ltd.	China
Iron liquicolor	Photometric CAB-Methode REF: 10229	Human Gesellschaft fur biochemia and diagnostica mbH	Germany
Magnesium liquicolor	Photometric REF: 10010	Human Gesellschaft fur biochemia and diagnostica mbH	Germany
Phosphorus liquirapid	Test UV photometric REF: 10027	Human Gesellschaft fur biochemia and diagnostica mbH	Germany
Zinc	Colorimetric method- ZINCO KIT. Code: CC02750	LTA s.r.l - s.u. -	Milano
Human Glutathione (GSH)	Sandwich technology-ELISA Kit. Cat.No：YHB1373Hu	SHANGHAI YEHUA Biological Technology	China

2.3. Statistical Analysis:

With SPSS version 21, evaluation of data was done. Mean ± Standard deviation was computed for descriptive statistics. To find significant differences between groups, independent sample t-tests were used. For instance, t-tests can be used to compare two groups (control vs. PD patients). P <0.01 indicates highly significant differences. Employing ROC curve and measurements, to achieve the sensitivity, specificity, and cutoff values of highly accurate discriminators in the patient group.

Ethical permission was granted by the Department of Scientific Affairs' Ethical Permission Committee.

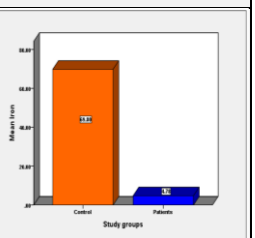
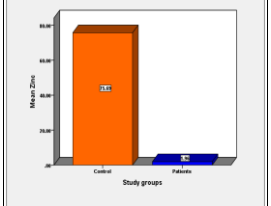
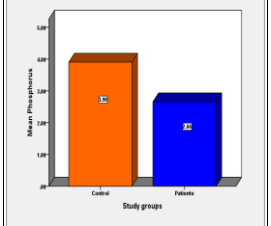
2. Results:

Table 1 describes a comparison of the assessed biochemical markers between the control group and patients. The results illustrate a highly significant decrease (P < 0.001) in the levels of all measured markers (except Mg, folic acid, and Homocysteine were highly significantly elevated (P< 0.001)) in the Patients group compared to the control group.

In Table 2, we review the distribution of males and females in the study groups, as well as the percentages of smokers and non-smokers in both groups.

The most sensitive and specific biochemical markers in Parkinson's patients have been identified using Receiver operating characteristic (ROC) analysis in Table 3 and Figure 2, and their role in diagnosing the disease or reducing its future effects was linked, which can be decisive and effective.

Table 1: Demonstration of the parameters in the study groups

	Study groups	Number	Mean	Std. D	Significance	
Iron Male (59-148) mg/dl Female (37-145) mg/dl	**Control**	**100**	**69.80**	**26.41**	**0.001***	
	Patients	**100**	**4.78**	**2.66**		
Zinc 70-115 µg/dl	**Control**	**100**	**75.69**	**21.44**	**0.001***	
	Patients	**100**	**1.96**	**0.53**		
Phosphorus Adults (2.5-5.0) mg/dl	**Control**	**100**	**3.90**	**1.05**	**0.001***	
	Patients	**100**	**2.66**	**1.05**		

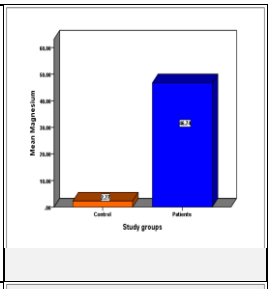
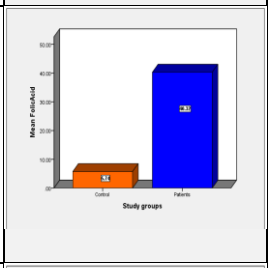
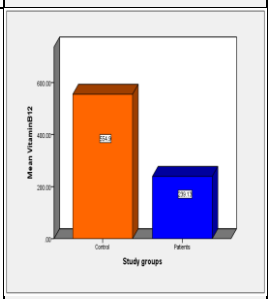
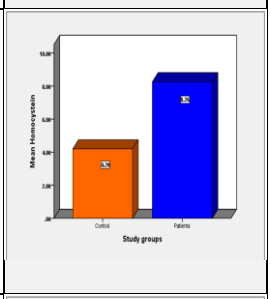
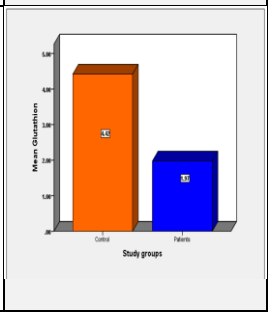
Magnesium Adult (1.6-3.0) mg/dl	**Control**	**100**	**2.27**	**0.65**	**0.001***	
	Patients	**100**	**46.74**	**24.11**		
Folic Acid (3 – 11) ng/ml	**Control**	**100**	**5.74**	**1.98**	**0.001***	
	Patients	**100**	**40.32**	**19.49**		
VitaminB12 (200 - 950) pg/ml	**Control**	**100**	**554.93**	**250.06**	**0.001***	
	Patients	**100**	**239.13**	**126.33**		
Homocysteine < 5 mmol/L	**Control**	**100**	**4.20**	**1.59**	**0.001***	
	Patients	**100**	**8.26**	**5.91**		
Glutathione 2 - 5 µM	**Control**	**100**	**4.42**	**0.75**	**0.001***	
	Patients	**100**	**1.97**	**0.86**		

Table 2: Demography of the Study

Parameters	Categories	Patients/number 100		Control/number 100	
		Frequency	Percent	Frequency	Percent
Sex	Female	59	59%	63	63%
	Male	41	41%	37	37%
Smoking	No	48	48	57	57%
	Yes	52	52%	43	43%

Table 3: ROC analysis of most discriminators in PD patients

Parameters	AUC	Sensitivity	Specificity	Asymptotic Sig. [b]	Cut-off Value
Magnesium	1.00	100%	100%	0.01	7.70
Folic Acid	0.999	98%	100%	0.01	10.65
Homocysteine	0.81	73%	82%	0.01	5.35

AUC: Area Under Curve

Null hypothesis: true area = 0.5b

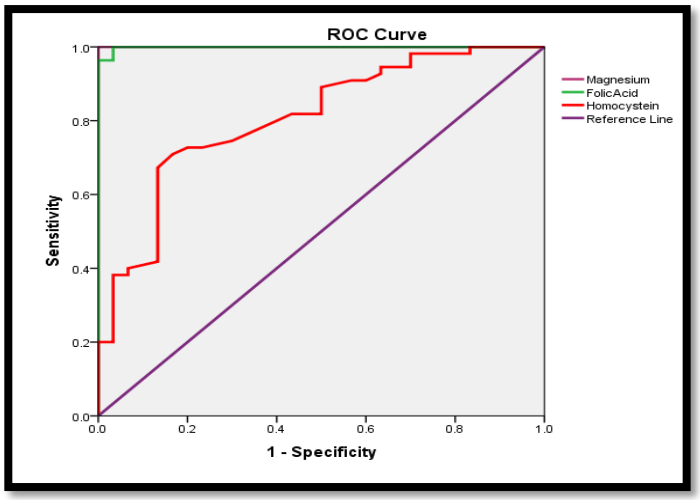


Figure 2: ROC curve of most discriminators in PD patients

4. Discussion:

Results of the present study identify significant deficiency (P<0.001) in phosphorus levels of patients compared to the control group. The progress in fibrillar aggregates (Lewy bodies) is the histological characteristic of PD. The main constituent of Lewy's bodies is α_synuclein, which is heavily phosphorylated and improperly aggregated. By consuming more phosphorus, this post-translational alteration increases α-synuclein toxicity and degeneration of dopaminergic neurons (19).

The present data shows a significant decrease (P<0.001) in the serum level of glutathione in patients compared to the control group. Glutathione depletion has been linked to the degeneration of PD because it impairs a cell's ability to digest waste products and damages its defenses against ROS & NS as well as hydrogen peroxide (22).

It is clinically important to note that mean ± SD (239.13±126.33) "normal-low" of vitamin B12 levels in this study quit within the reference limit of serum vitamin B12, but statistically highly significant decrease in patients in comparison to the control group. This suggests that there is a greater demand for vitamin B12 in a disease condition and, to some degree, reflects the negligible sensitivity of the blood vitamin B12 measurement (23) may clarify why peripheral neuropathy, cognitive decline, and a faster pace of disease development are linked to low vitamin B12 levels (24).

Our results display significantly increased (P<0.001) serum level of Homocysteine in the patients group in comparison to healthy control persons, because the conversion of L-dopa to 3-O-methyldopa needs CH3-donation from S-adenosyl-methionine (comprising catechol-O-methyl-transferas), which results in higher levels of S-adenosyl Homocysteine, which is quickly broken down to form Homocysteine, this clinical elevation may be caused by the patients' L-dopa treatment (25). However, another research by Zoccolella et al. demonstrates that Homocysteine maintains some neurotoxic processes linked to the pathophysiology of PD neurodegenerative disorders (26). However, additional research shows that vitamin B12 and folate deficiencies, as well as hyperhomocysteinemia, are not risk factors for the illness (27). Our results are consistent with research by Di Francisco-Donoghue and his colleagues found that people with P's D of elevated Homocysteine and lower levels of glutathione (28).

This study expresses significantly decreased serum iron in the disease's group (P< 0.007) which is clinically lower than the normal and this is compatible with several studies on the connection between anemia and PD since low hemoglobin was found to be a risk factor and involve in the pathophysiology of PD, and low iron (resulting from disrupted metabolism) causes anemia (29). Moreover, anemia may indicate a vitamin B12 deficit in PD patients (30), or impaired absorption of other nutrients, which leads to the creation of reactive oxygen species, which causes disease-related neurodegeneration (31).

Also, we found there is a significant decrease (P<0.001) serum level of Zinc in the patient's group in comparison to the control group, this result was confirmed by another meta-analysis (32). Since Zn is vital for many proteins and enzymes, such as interleukins, metallothioneins, and superoxide dismutase, which are involved in oxidative stress and inflammation, the association between low circulating Zn amount and PD can be expressed by its antioxidant properties. The human PARK9, a transporter for lysosomal confinement cytoplasmic Zn linked to autosomal recessive early-onset PD, is another mechanism explaining the lack of intracellular Zn2+ homeostasis. When PARK9 activity is lost, intracellular zinc homeostasis is upset, which in turn causes lysosomal dysfunction, α-synuclein buildup, and mitochondrial malfunction (18).

The present study detects a highly significant increase in serum level of folic acid and Hcy in Patients compared to the control group but this is not compatible with the study of Adina Turcu-Stiolica et al, as they conclude that dietary intake of folic acid decreased the dimensions of homocysteine (33).

5. Conclusion:

Validation of certain biomarkers, such as glutathione and Homocysteine assays, for PD development to identify individuals in the early stages of the illness. Additionally, keeping blood levels of folic acid and vitamin B12 within normal limits may help monitor Parkinson's disease.

Future Directions:

Research on PD prevention is still a major priority. There will need to be an international effort to lower exposure to environmental toxicants and enhance lifestyle choices, along with attempts to address current discrepancies across sex, race, ethnic group, economic position, and geography. Finding genetic alterations will yield new information, particularly in groups that have not received enough attention. Technological developments might enhance therapy, monitoring, and screening.

With high sensitivity and specificity, biomarkers for aberrant α-synuclein can differentiate between healthy controls and people with various neurologic disorders as well as those with clinically diagnosed PD, dementia with Lewy bodies, or REM sleep behavior disorder.

Further research is necessary to elucidate how magnesium affects α-synuclein aggregation in vivo tests under both elevated and deficient magnesium

settings. Gaining knowledge of this link may help one better understand the pathogenic mechanisms behind PD and possible treatment approaches.

Due to the disease's heterogeneity, small sample sizes, and the difficulty of accounting for confounding variables like genetic variability, comorbidities, and patient lifestyle differences, one major limitation in PD research is the difficulty in establishing clear cause-and-effect relationships.

Conflict of interest:

The author declares no conflict of interest.

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