The Role of Adropin as a Novel Biomarker in Iraqi Patients with Parkinson's Disease and Osteoporosis

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Abstract

Adropin, a 4.9 kDa peptide encoded by the energy homeostasis associated gene (Enho) on chromosome 9, is synthesized by a number of organs including the central nervous system (pia mater, neurons neuroglial cells, Purkinje cells, granular layer, and vascular area), the kidney, heart, pancreas, liver and the human umbilical vein. Adropin's half-life is unknown at the moment, however it might last anywhere from a few minutes to half an hour, which is similar to other secretory proteins. Adropin's biological actions are mediated by the orphan G protein-coupled receptor 19 being activated (GPR19).

The focus of this research was to evaluate serum adropin rates in Patients with parkinson with osteoporosis disease and in Parkinson's patients without osteoporosis disease, and to analyse the outcomes with control groups, as well as to investigate the relationship between Adropin levels and anthropometric and clinical features (age, gender, BMI), serum parathyroid hormones (vitamin D3, calcium, and phosphorous), and glucose. Eighty people participated in the experiment and were divided into two groups. Parkinson's disease patients with osteoporosis illness (G1), Parkinson's disease patients without osteoporosis disease (G2), and control participants (G3) All of the research participants came from the Specialized Center for Parkinson's Disease with Osteoporosis in Baghdad/Alrisafa. G1, G2, and G3 were between the ages of 55 and 67, 38 and 75, and 55 and 66, respectively. In all of the groups surveyed, the ratio of males to females is increasing. This can be linked to the fact that males have a higher incidence and prevalence of Parkinson's disease than females. The results showed that the mean mean serum Adropin values in G1 (586.020 ±17.858 pg/mL) and G3 (584.572± 34.022 pg/mL) were considerably higher (P=0.0001) than the mean serum adropin in G2 (216.928±26.032 pg/mL), while the mean serum adropin in G1 (586.020± 17.858 pg/mL) was slightly higher than the mean serumG3. The investigation also included an examination of the Receiver Operating Characteristic (ROC) curves for blood adropin levels when used as a test to divide people into cases and controls, as well as a calculation of the "cut-off value" for diagnosing the condition with the best specificity and sensitivity.

Key Words: Adropin, Parkinson's Disease, Osteoporosis Disease, ROC.

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Introduction

The second most common neurodegenerative illness is Parkinson's disease (PD). The presence of Lewy bodies, which are caused by a buildup of -synuclein, results in the loss of dopamine-regulated motor circuits, increasing immobility, and a variety of non-motor symptoms. Patients with Parkinson's disease experience more hospitalizations, take longer to recover from comorbidities, and have a higher death rate than healthy controls.

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Secondary osteoporosis has been observed frequently and is associated with a poorer prognosis, despite the fact that it is generally neglected. The aging population continues to grow at an unprecedented rate over the world. Up to 12.5 percent of the overall population is presently over 65 years old, with nearly 17 percent of the global total expected to be over 65 years old by 2050 (Kinsellak, 2009). The increasing risk of neurological and bone disorders is one of the many public health and socioeconomic issues that this aging trend brings. Parkinson's disease (PD) is the second most often documented neurological illness, with an estimated frequency of 1% among those over 60. Furthermore, the economic burden of Parkinson's disease is increasing (Hiorth, Y.H. 2013). As Parkinson's disease proceeds, neurological degeneration causes widespread lesions in the brain, as well as balance problems and a higher chance of falling. Motion impairments and non-motor related dysfunction, dementia, gastrointestinal disorders, body composition changes, falls, and a significantly increased risk of fracture, as well as poor bone mineral density, are all indicators of PD's systemic character (Jankovic, J. 2008, Chen, H. 2003). The amount of scientific into the pathophysiology of Parkinson's disease has centered on the mechanisms of PD advancement in the substanta nigra and their neurologic implications; nevertheless, very little recognized about how PD affects comorbidities, especially its relationship with bone mass and osteoporosis, a significant complication of long-term PD.

Adropin is a 4.9 kDa peptide diverse range of organs such as the central nervous system (neurons, neuroglial cells, pia mater, vascular area, Purkinje cells, and granular layer), heart, kidney, liver, pancreas, and human umbilical vein, which is recorded by the energy homeostasis related gene (Enho) on chromosome 9 (Shahjouei, S. (2016)).

Adropin's half-life is unknown at the moment, however it might last anywhere from a few minutes to half an hour, which is similar to other secretory proteins. (D. Thapa, M.W. 2018) Adropin's biological actions are mediated by the orphan G protein-coupled receptor 19 being activated (GPR19) (Stein, L.M., 2016; Thapa, De., 2018).

Materials and Methods

Study design and subjects: Eighty patients take part in this research and were dividded into three groups: G1: Parkinson with Osteoporosis, include (14) patients, (7) of them are males and (7) of them are females G2: Parkinson without Osteoporosis, consists of (36) patients Parkinson disease, (28) of them are males and (8) are females. And G3: consists of (30) subjects, (17) of them are males and (13) are females control subjects. Prospective study has been carried out at Specialized Center for Parkinson with osteoporosis disease in Baghdad during the period between February 2021 and July 2021. All patients' gender distributions demonstrate an increase in the male to female ratio. Ten milliliters of venous blood were taken from research participants and a control sample was deposited in a plain tube and kept at room temperature for 15 minutes before being centrifuged at 4000rpm for 10 minutes to extract serum, which was refrigerated at (-20^{o}C) unless utilized right away. Age, gender, BMI, Adropin, PTH, Ca^{+2} Phosphorous, and vitamin D3 are all factors to consider. The individuals' BMI was determined by multiplying their weight (kg) by their height squared (m^2).

Serum Levels measurement: Enzyme linked immunosorbent assay (ELISA) Kits are used to evaluate Adropin levels (Human AD, ELISA Kit).

Results & Discussion

The mean serum adropin in G1 (586.020± 17.858) pg/mL was substantially close (P = 0.0001^) to the mean serum adropin in G3 (584.572± 34.022 pg/mL), whereas the mean serum adropin in G1 (586.020± 17.858) pg/mL was higher than the mean serum adropin in G2 (216.928± 26.032 pg/mL) as shown in figures (1). No study has yet addressed the relationship of adropin with Parkinson's disease or osteoporosis, so further studies are needed. Table 2 shows that the mean serum parathyroid in G1 (225.894±28.960pg/mL) was markedly close (P=0.0001^) to the mean serum parathyroid in G3 (253.275±51.616pg/mL), whereas the mean serum parathyroid in G1 (225.894±28.960ng/mL) was mildly greater than the standard serum parathyroid in G2 (199.952±18.749pg/mL). Because steroids suppress calcium absorption from the intestinal tract and calcium reabsorption from the renal tubules, steroid treatment can cause secondary hyperparathyroidism in a compensatory manner, speculate that rapid reduction of the steroid dose can cause hysteria, because steroids suppress calcium absorption from the intestinal tract and calcium reabsorption from the renal tubules, steroid treatment can cause secondary hyperparathyroidism in a compensatory manner,

(Abdo, W.F., Van De, 2010). Parathyroid hormone is another biological sign that might influence PD symptoms development (PTH) (Agyekum, H.A. 2018). Furthermore, it appears that the intensity of PD symptoms is linked to parathyroid gland function. Table 2 shows that the mean serum calcium in G1 (10.562±0.465 mg/mL) was extremely significantly (P=0.0001) higher than the mean serum calcium in G3 (9.425±0.630 mg/mL), whereas the mean serum calcium in G1 (10.562±0.465 mg/mL) was somewhat higher than the mean serum calcium in G2 (10.249±0.670 mg/mL). Various biochemical indicators have been linked to the etiology of Parkinson's disease in numerous investigations (Moustafa. A.A., 2016, Seppi, K (2019)). Calcium, which plays a vital role in the activity of neurons and is involved in the transmission of the depolarizing signal and synaptic activity, is one of the most essential components linked to PD (Armstrong, M.J., & Okun, M.S. 2020). Furthermore, calcium dysregulation has been implicated in the etiology of Parkinson's disease in various studies (Tehrank, S.S., Sarfi, M, Yousefi 2020). Parkinson 's illness is a multifactorial ND characterized by a variety of molecular and neural abnormalities, including autophagy and mitochondrial disruption, ER stress, and calcium hemostasis deregulation, all of which lead to Dopaminergic (DA) neural death in the Substansa Nigra (SNs) in the midbrain (Michel, P.P 2016). In SNs, the loss of calcium hemostasis results in neural cell death. Mitophagy disruption, ER stress, mitochondrial dysfunction, and -synuclein aggregation may all contribute to abnormal calcium hemostasis in DA neurons. The survival of DA neurons has been found to be reduced when calcium levels are high or low. Multiple molecular diseases, such as NMDA receptor overactivity, can disrupt calcium balance in DA neurons. Calcium stimulates excessive dopamine production in DA neurons, resulting in autointoxication (Tehrank, S.S., Sarfi, M, Yousefi 2020). Table 2 shows that the mean serum phosphorus in G1 (2.768±0.836 mg/dL) was slightly higher (P=0.0001) than the mean serum phosphorus in G3 (1.549± 0.784 mg/dL), while the mean serum phosphorus in G1 (2.768±0.836 mg/dL) was significantly lower (P=0.0001) than the mean serum phosphorus in G2 (6.991±11.396 mg/dL). Several researchers have associated biochemical markers like phosphorus to PD and concluded that the variance in phosphorus serum levels between the two groups was not significant (Qader, A., & Qader, A. 2020; Tehrani, S.S., 2020). According to the study's findings, there was a substantial difference in phosphorous serum levels between the two groups. Furthermore, lower phosphorus levels were linked to a higher incidence of Parkinson's disease, while the current research found a substantial variation in serum phosphorus levels between three gropes (Qader, A., & Qader, A. 2020). Previous research has linked phosphorus in the blood to Parkinson's disease, with a very significant drop (p<0.001) when compared to the control group. The mean serum vitamin D3 in G1 (25.013±2.044pg/mL) was slightly higher (P=0.0001) than the mean serum Vit. D3 in G3 (24.431±1.531pg/mL), whereas the mean serum vit D3 in G1 (25.013±2.044pg/mL) was higher than the mean serum vit D3 in G2 (21.546±0.801pg/mL). The absence of blood vitamin D levels and recollection bias make it extremely difficult to draw clear conclusions from this study. Furthermore, outdoor physical activity was utilized as a surrogate for vitamin D status, despite overwhelming evidence that physical exercise lowers the incidence of Parkinson's disease, which is a possible confounder in this investigation (Fang, X., Han, D., 2018). There has been no evidence of a link between vitamin D levels and the development of Parkinson's disease. In contrast to the Finnish research, an analysis of over 13,000 men and women from the perspective Atherosclerosis risk in communities (ARIC) study cohort revealed no link between baseline vitamin D levels and the risk of Parkinson's disease. After 17 years (Shrestha, S., Lutsey, 2016). Previous research has linked vitamin D 3 levels in the blood to Parkinson's disease, with a very significant drop (p<0.001) when compared to the control group (Alsadi, A.M., Alouweisi2018). while the current investigation found a substantial drop (p=0.0001^) in vitamin D3 levels in three groups. The mean serum glucose in G1 (61.262-150.511 pg/mL) was somewhat lower (P=0.0001) than the mean serum glucose in G3 (67.493-194.497 pg/mL), whereas the mean serum glucose in G1 (61.262-150.511 pg/mL) was lower than the mean serum glucose in G2 (118.013-236.657 pg/mL). Patients with type 2 diabetes mellitus (T2DM) have an increased chance of acquiring Parkinson's disease (PD) (Yue, X., Li, H., Yan 2016). Experiments have shown that prolonged hyperglycemia causes dopaminergic impairment in the elderly (Renaud, J., Bassareo 2018), the presence of DM may cause cognitive impairment 9LI, W, Risarcher, S.L. 2016). &

e diagnosis of Parkinson's disease happens when the disease has advanced to a point when motor characteristics are plainly seen and considerable neurological damage has already occurred (Noyce, A.J. Less, 2016).

Table 1. Serum levels of Adropin in G1, G2 and G3

Parameter	Parkinson's disease & Osteoporosis patients n=14	Parkinson's disease without Osteoporosis patients n=36	Control	P value
Adropin (pg/mL)	**586.020±17.858 (553.597-612.900)**	**216.928±26.032 (125.257-249.541)**	**584.572±34.022 (521.188-669.623)**	**0.0001^**

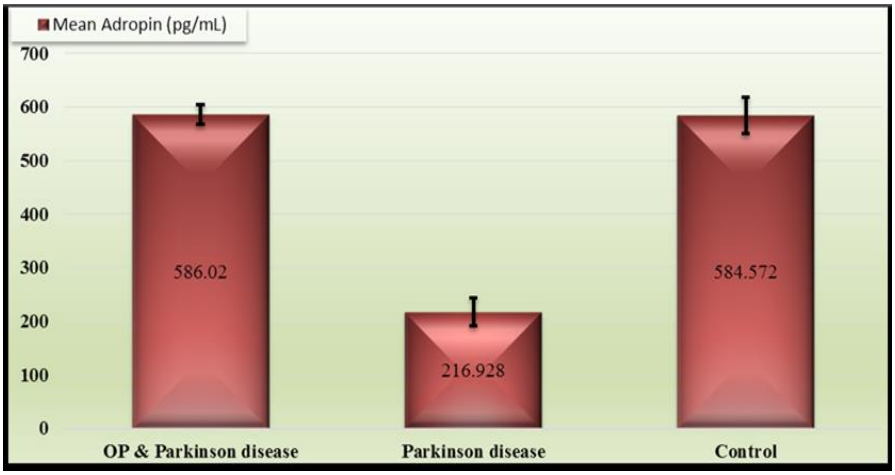

Figure 1. Mean values of serum adropin hormone levels in G1: Parkinson's with osteoporosis, G2: Parkinson without osteoporosis, and G3: control.

Table 2. Serum levels of (Ca, phosphorus, PTH, vit D3 and Glucose) in G1, G2 and G3

Parameter	Parkinson's disease & Osteoporosis patients n=14	Parkinson's disease without Osteoporosis patients n=36	Control N=30	P value
Parathyroid (pg/mL)	225.894±28.960 (174.738-292.984)	199.952±18.749 (174.055-236.933)	253.275±51.616 (191.970-385.404)	0.0001^
Ca (mg/dL)	10.562±0.465 (9.675-11.060)	10.249±0.670 (6.932-11.165)	9.425±0.630 (8.182-10.444)	0.0001^
Phosphorus (mg/dL)	2.768±0.836 (1.389-4.592)	6.991±1.396 (5.138-9.780)	1.549±0.784 (0.586-3.547)	0.0001^
Vit D3 (ng/ml)	25.013±2.044 (22.676-27.625)	21.546±0.801 (19.788-22.939)	24.431±1.531 (22.722-27.561)	0.0001^
Glucose (mg/dL)	110.895±32.011 (61.262-150.511)	171.514±23.891 (118.013-236.657)	105.364±31.594 (67.493-194.497)	0.0001^
#Significant difference between two independent means using Students-t-test at 0.05 level.				
^Significant difference among more than two independent means using ANOVA-test at 0.05 level.				

Receiving Operating Characteristic (ROC) for Adropin

The area under the curve (AUC) of serum Adropin (pg/ml) was 0.5 with confidence interval (95 percent CI) and lower bound (0.289) and upper bound (0.289) when used as a test for diagnosing subjects into Parkinson with osteoporosis disease cases (G1) and control groups (G3), according to the ROC curves analysis (0.711). However, when serum Adropin levels were employed as a test for diagnosing Parkinson without osteoporosis disease patients (G2) and controls (G3), the area under the curve (AUC) of serum Adropin levels was shown. The AUC of serum Adropin (pg/mL) was 1.000, with a 95 percent confidence interval (CI) and lower and upper bounds (-).

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