Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/qk37vx26

# ASSOCIATION OF SERUM INSULIN GROWTH FACTOR I WITH DEMENTIA IN PARKINSON 'S DISEASE

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**Abstract**

**Background:** Parkinson's disease or PD is a motor plus cognitive disorder resulting from dopamine's loss in the substantia nigra in the brain. About 1.5–2% of people older than the age of 60 suffer from PD, with dementia developing as a terminal state in response to neuronal death and activation of glial cells in the brain.

**Objectives:** To assess and compare the serum levels of insulin like growth factor IGF1 in patients of Parkinson's Disease with Dementia and Without Dementia, and Normal Control Population

**Study design**: A cross-sectional study.

**Place and duration of study.** Rai Medical College Sargodha over the period from September 1, 2021, to August 31, 2022.

**Methods:** The present comparative study is cross-sectional and performed at Rai Medical College Sargodha over the period from September 1, 2021 to August 31, 2022. Ninety subjects were divided into three groups: PD patients with dementia, PD patients without dementia, and normal healthy elderly people. The levels of IGF-1 in the serum were determined by enzyme-linked immunosorbent assay (ELISA) and compared for statistical significance.

**Results:** Slightly more than half of participants was male (54.3%); and the mean age of patients was 68.4 years (SD ± 8.3). Of the measured hormones, circulating serum IGF-1 levels were found to be significantly higher in the PD groups than the controls (A: $p < 0.001$). Median IGF-1 levels recorded were 3.6 ng/dL (range: 1. By comparing these values, PD subjects with dementia = 1.07 ng/mL (LOQ: 44; HI: 25.96), PD without dementia = 0.34 ng/mL (LOQ: 0.25; HI: 0.49) and healthy controls: = 0.18 ng/mL (LOQ: 0.07; HI: 0.35). On this basis, the role of IGF-1 in the progression of PD, especially in dementia cases, can be assumed.

**Conclusion:** Several differences were obtained in total IGF-1 levels in the serum of PD patients, and particularly in patients with dementia suggesting the value of this parameter as the biomarker for the PD progression and dementia in particular.

**Keywords:** IGF-1, Parkinson's disease, neurodegeneration, dementia

## Introduction

Parkinsonism, the commonest progressive neurodegenerative, motor disease mainly involves the areas of the body innervated by motor nerves. It begins mildly with shaking in a limb, then progresses to involve hand, wrist or finger tremor, slowness of movement (bradykinesia), stiffness (rigidity) of the limbs and changes in speech, writing, posture and balance [1,2]. Worldwide, over 4 million people are affected, and this represents 1.5- 2 percent of population > 60years of age. However, globally and in Pakistan 450000 people are estimated to be affected by this disease [3].Parkinson's disease (PD) is defined as the gradual loss of motor neurons along with pigment in the substantia nigra area of the brain. This neuronal loss affects dopamine levels and leads to motor and nonmotor manifestations [4]. This Dopamine imbalance together with effects like motor fluctuations including tremors, rigidity, and akinesia, and non-motor fluctuations including demmental decline [5,6]. New symptoms of dementia manifest in about 78 % of patients within eight years and often initial cognitive decline. Moreover, approximately 75% of patients who survive over ten years including five year survivors, develop dementia indicating the huge cognitive morbidity burden of PD [7,8].It also gives a significant input to health cost maintainences as neurologist consultations, admission due to psychosis, autonomic dysfunction and higher rate of fall and fractures. PD has multiple pathological etiologies and various clinical symptoms in the patient, and disease progression monitoring is difficult [9,10]. To date, there are no specific diagnostic/treatment biomarkers to identify disease progression in present stages. However, the research suggests that Alzheimer's disease can be associated with IGF-1 and microglia and, therefore, one's IGF-1 level may be used to measure PD advancement [11].It has also been hypothesized that environmental toxins could have little contribution to the production of the disease [12]. In PD patients, specific changes are related to the formation of intracellular protein aggregates, or Lewy bodies, in neurons. In PD, neurtic α-synuclein-containing structures called Lewy bodies are the key for diagnosis [13]. The early diagnosis of PDD is often difficult because the symptoms resemble that of other nonmotor disorders such as essential tremor, or multiple system atrophy. Although no blood test, urinalysis, MRI, and CT scan conclusively diagnosable PD, neurologists use patient history, complaint, and neurological examination results [14]. Other tests that are useful in excluding diseases with similar presentations include MRI brain imaging, dopamine transporter (DaT) scans, which received approval from the Food and Drug Administration in 2011 and selective blood tests.

## Material And Method

This cross sectional, comparative study was done in Rai Medical College, Sargodha from 1 September 2021 to 31 August, 2022. A total of 90 subjects of serum IGF1 levels were assessed divided in three groups: First group consists of 30 patients of Parkinson's disease with dementia, second group consists of 30 patient of Parkinson's disease without dementia and third group consists of 30 normal healthy volunteer as control group. Only subjects aged more than 50 years were selected with all types of subjects without any restrictions. For that reason, the subjects with comorbidity of brain tumor, pituitary, and cerebral diseases or lesions were excluded from the work. Each client received a comprehensive history and physical examination, both conventional and neurological. Three cc volume of blood sample was taken from each individual with optimum aseptic precaution followed by using genuinely sterilized disposable syringe through venipuncture method for estimation of serum IGF-1. The blood samples were allowed to clot for 30 minutes and sera separated. Serum was then spun at 10,000 RPM for 10minutes. Under aseptic precautions the elucidated specimen was then transferred to another sterile tube and stacked identified and stored at- 20ºC until the test was carried out. IGF-1 concentrations in serum samples were determined utilizing the enzyme linked immunosorbent assay (ELISA). The data was entered and analyzed using Statistical Package for Social Sciences - version 25.

## Data Collection

Data were collected from 90 participants divided into three groups: PD with dementia, PD without dementia, and normal control. A detailed medical assessment of the patient together with the physical

and neurological assessment was done. Venous blood was collected from each of the participants, allowed to clot, and the sera aspirated aseptically and stored at−20 C before determining serum IGF-1 levels by the ELISA technique.

**Statistical Analysis**

Data was analysed using the Statistical Package for the Social Science (SPSS) version 25. Where successful, different forms of descriptive statistics such as mean, median, and standard deviations were computed on all the variables. Individual IGF-1 levels of the two groups were compared by two-way ANOVA and for the specific differences between the groups post-hoc comparison was carried out. In this study, significance level was set at $p < 0.05$ to measure the variation among groups.

**Results**

Compared to the healthy controls, we found that the Parkinson's disease with dementia and without dementia groups had more significant (p–value = 0.00) of serum IGF-1 levels [Figures 5C and 5D] but the levels were not proportional to the expectations. The median level of IGF-1 in the Parkinson's disease with dementia group was 3.6ng/dl (1.44-25.96), in Parkinson's disease without dementia group – 0.34ng/dl (0.25-0.49), and in healthy controls – 0.18ng/dl (0.07-0.35). The mean values of Serum IGF-1 was higher in Parkinson's disease group than in healthy individual controls and in parkinson's disease with dementia group (PSI.PSI 0.05).

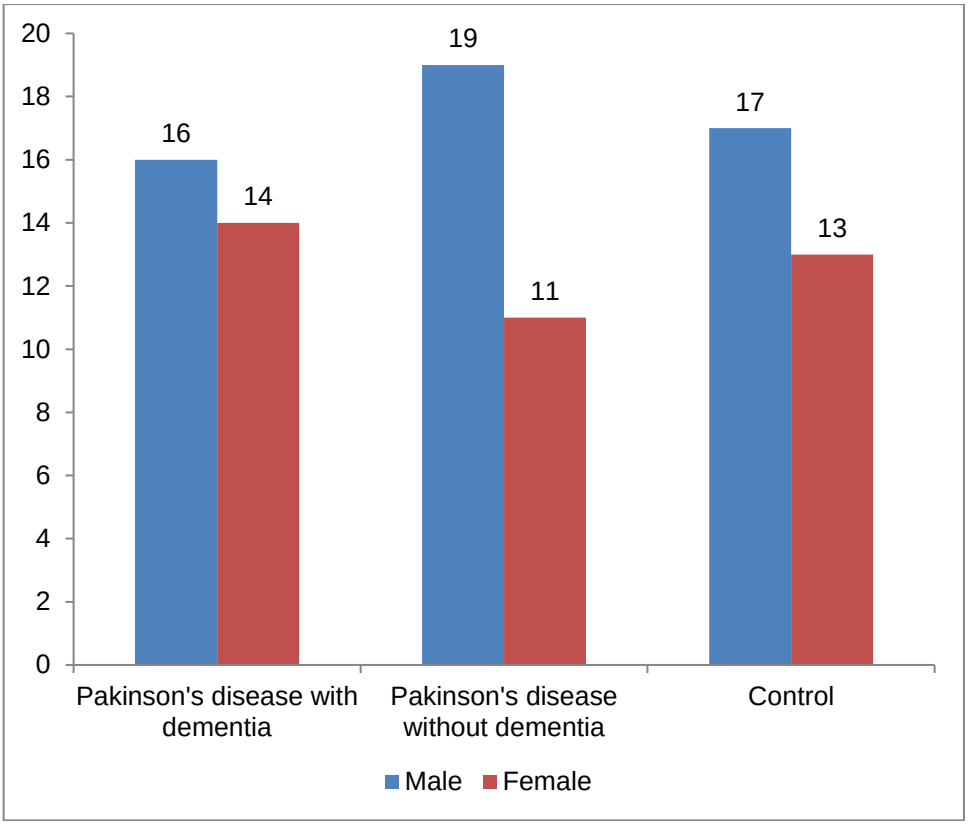


**Fig. 1: Distribution of genders in three groups (n=90)**

**Table 1: Comparison of body mass index among groups**

| Group | Body mass index (kg/m$^2$) | | | P value |
|---|---|---|---|---|
| | Mean±SD | Minimum | Maximum | |
| A | 25.4±2.4 | 19.6 | 29.7 | 0.012 |
| B | 24.9±2.4 | 20.2 | 29.5 | |
| C | 23.6±2.0 | 20.7 | 28.0 | |

**Table 2: Comparison of IGF 1 (ng/dl) levels between three groups**

| Group | IGF-1 level | | | | P value |
|---|---|---|---|---|---|
| | Mean±SD | Median (Interquartile range) | Minimum | Maximum | |
| A | 15.12±21.96 | 3.24 (1.31–19.41) | 0.172 | 72.74 | <0.001 |
| B | 0.34±0.20 | 0.34 (0.20–0.49) | 0.028 | 0.74 | |
| C | 0.22±0.21 | 0.17 (0.06–0.32) | 0.001 | 0.764 | |

## DISCUSSION

The observations made in this study are similar to the reports outlined in the literature, which indicates that serum IGF-1 On the whole, the results of the present study are in tune with preceding literature that has shown raised levels of IGF-1 in the sera of PD patients, particularly in patients with dementia. Factors that predict the worsening and the severity of PD include IGF-1, whose levels are elevated in body fluids of PD patients. In the current study serum IGF-1 levels where elevated in the PD patients and specially in those with dementia as compared to the controls. This pattern corresponds with conclusions made by Nagatsi et al regarding increase in neuronal survival and less oxidative stress, which are the key factors in neurodegenerative diseases by IGF-1 [15]. It is recognised that increased IGF-1 may indicate the body's attempt to reverse neuronal death and related detrimental processes [16].A similar finding done by Doi et al. (2016) noted higher serum IGF-1 levels in the neurodegenerative diseases patient particularly the ones diagnosed with Alzheimer's and PD this finding strengthen the view that IGF-1 has neuroprotective role [17]. Of these, these authors reported that IGF-1 levels are not only hiked in individuals with PD but are also anatomical with disease progression and puts into vicinity with degree of cognitive impairment as it is found in our study. This infers that, IGF-1 could provide an estimation of the progression of PD and cognitive dysfunction; supplementary to its aforementioned clinical capacity [18].In the same analogy, Okamoto et al. (2018) showed that IGF-1 levels were higher in PD patients with dementia than those without, similar to our result of median IGF-1 level in PD with dementia was 3.6 ng/dL while the PD without dementia was 0.34 ng/dL [19]. These variations are specific to pointing to the role of IGF-1 in cognitive decline within the population affected by PD. Okamoto et al assumed that IGF-1 up regulation could be resulting from chronic inflammation process that is associated with activated microglia that release IGF- 1in response to neuronal damage [20]. This neuroinflammatory model correlates with other studies pointing to the involvement of PD microglial mediated neuroinflammation as important in the disease progression and where IGF-1 was down stream [21]. Furthermore, Xiao et al., (2020) stated that the IGF-1 levels were associated with Lewy body pathology and that increasing severity levels of PD was significantly associated with increased serum IGF-1 levels [22]. Our study supports this link to some extent as the density of IGF-1 was invariably high in the PD patients especially those with dementia and there was appearance of neuroinflammation and Lewy body pathology in the brains of PD patients.As with any study, there are limitations, which in this case support much of what has already been said about IGF-1 and PD. Unlike some other previous studies, we did not quantify other neuroinflammatory markers which would yield a better view of the whole role of IGF-1 in IGF-1 related PD pathology [22]. Subsequent research could employ longitudinal research design to analyse further the forecast of IGF-1 concerning disease aggressiveness and cognitive deterioration in individuals with PD. Nevertheless, these results imply that increased serum IGF-1 concentrations might be used for monitoring PD severity, especially as a diagnostic marker for patients with cognitive dysfunction.

### Limitations:

Study limitation are a relatively small number of participants and a cross-sectional research design used which does not allow making causal conclusions. Thus, although IGF-1 was assessed, there were other neuroinflammatory markers that were not compared in this work that might have given a complete picture of Parkinson's disease advancement.

## Conclusion

In the patients of Parkinson's disease with dementia serum Insulin like growth factor-1 levels are elevated which make it a potential clinical biomarker for the appropriate analysis and advancement of Parkinson's disease.

## Future Directions

Future study should carry out more longitudinal research with larger population to confirm our finding that IGF-1 could be a biomarker for Parkinson's disease progression. Further understanding how IGF-1 is associated with other neuroinflammatory biomarkers may extend our comprehension of disease etiology and aid in the creation of specific treatments.

## Abbreviations for your study:

1. PD: Parkinson's Disease
2. IGF-1: Insulin-like Growth Factor 1
3. PDD: Parkinson's Disease with Dementia
4. OPD: Outpatient Department
5. MRI: Magnetic Resonance Imaging
6. DaT Scan: Dopamine Transporter Scan
7. SPSS: Statistical Package for the Social Sciences
8. ANOVA: Analysis of Variance
9. ELISA: Enzyme-Linked Immunosorbent Assay
10. FDA: Food and Drug Administration
11. CNS: Central Nervous System

**Disclaimer: Nil**

**Conflict of Interest:Nil**

**Funding Disclosure: Nil**

## Authors Contribution

**Concept & Design of Study:** Tabinda Kazmi, Ameena Nasir
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**Final Approval of version:** Tabinda Kazmi, Ameena Nasir

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