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B Shivani
Department of Pharmacy Practice, Care College of Pharmacy, Hanamkonda, Warangal, Care College of Pharmacy, Oglapur (v), Damera (m), Warangal rural, Telangana, India

K Nageswari Devi
Department of Pharmacy Practice, Care College of Pharmacy, Hanamkonda, Warangal, Care College of Pharmacy, Oglapur (v), Damera (m), Warangal rural, Telangana, India

V Manasa
Department of Pharmacy Practice, Care College of Pharmacy, Hanamkonda, Warangal, Care College of Pharmacy, Oglapur (v), Damera (m), Warangal rural, Telangana, India

Om Prakash Prasad
Sri Sri Neuro Centre, Hanamkonda, Warangal, Care College of Pharmacy, Hanamkonda, Warangal, Care College of Pharmacy, Oglapur (v), Damera (m), Warangal rural, Telangana, India

Anirudda Deshpande
Sri Vinayaka Neuro Centre, Hanamkonda, Warangal, Care College of Pharmacy, Hanamkonda, Warangal, Care College of Pharmacy, Oglapur (v), Damera (m), Warangal rural, Telangana, India

D Sudheer Kumar
Department of Pharmaceutics, Care College of Pharmacy, Care College of Pharmacy, Hanamkonda, Warangal, Care College of Pharmacy, Oglapur (v), Damera (m), Warangal rural, Telangana, India

P Kishore
Head, Department of Pharmacy Practice, Care College of Pharmacy, Hanamkonda, Warangal, Care College of Pharmacy, Oglapur (v), Damera (m), Warangal rural, Telangana, India

Correspondence
P Kishore
Department of Pharmacy Practice, Care College of Pharmacy, Hanamkonda, Warangal, Care College of Pharmacy, Oglapur (v), Damera (m), Warangal rural, Telangana, India

Estimation of serum uric acid levels in Parkinson's disease patients along with their comorbidities and treatment pattern

B Shivani, K Nageswari Devi, V Manasa, Om Prakash Prasad, Anirudda Deshpande, D Sudheer Kumar and P Kishore

Abstract
To find association of uric acid levels in patients with Parkinson's disease and its severity. To study the affect of different Comorbid conditions and treatment patterns in Parkinson's disease patients. A Prospective observational study among 84 patients with Parkinson's disease was carried out. Serum uric acid levels were determined and association among uric acid levels with disease severity in Parkinson's disease patients was evaluated using Hoehn and Yahr staging scale. Out of 84 patients, Serum uric acid test was done in 60 patients. Among them 65% were found with uric acid levels less than median value 5.5 mg/dL and 56.6% were found in early stage, 11% were found in advanced stage Parkinson's disease. In our study, we found inverse association of uric acid levels and its significant correlation with disease severity in early and advanced stage Parkinson's disease patients. Comorbid condition such as hypertension may be associated with a moderate to severe decline in motor functions. Majority of the patients were treated with Trihexyphenidyl, Carbidopa & Levodopa, Rasagiline. Clinical pharmacist should identify whether the dyskinesia occurred in the patient is drug induced or disease related. This could help physician to provide fractionised dose of Levodopa/Carbidopa for patients and prevent adverse drug reactions.

Keywords: Parkinson's disease, uric acid, hoehn and yahr staging, trihexyphenidyl, levodopa / carbidopa

1. Introduction
Parkinson's disease (PD) is a neurodegenerative disorder that affects predominately dopamine-producing ("dopaminergic") neurons in a specific area of the brain called substantia nigra. More than 10 million people worldwide are living with PD. Incidence of Parkinson's disease increases with age, but an estimated four percent of people with PD are diagnosed before age 50. Motor symptoms of PD may include pill rolling tremor, bradykinesia, muscle rigidity, micrographia, hypophonia, hypomimia, stooping or hunching over whereas non motor symptoms include cognitive changes, constipation, hallucinations, delusions and sleep disorders. There is evidence that both genetic and environmental factors are important determinants and family history of the disease has been shown to be a risk factor. Some specific risk factors include age, gender, head injury, area of residence, occupation, pesticide exposure and exposure to metals.

Although the cause of neurodegeneration is thought to be multifactorial, there is evidence to support oxidative stress as a main factor.In cellular models of neurodegeneration, urate has been demonstrated to reduce oxidative stress, mitochondrial dysfunction and cell death occurring spontaneously in culture or induced by pesticides, glutamate and iron ions. Urate has also been demonstrated to reduce oxidation of dopamine in caudate and substantia nigra of PD patients. Urate is, in fact, a powerful scavenger of peroxyl radicals (ROO•) and hydroxyl-radicals (OH•), and is able to inhibit free radical-initiated DNA damage.

Based on its known antioxidant and metal-complexing properties, and its relatively high levels in humans, urate could serve as an endogenous defense against the development and progression of PD. Researchers have found that men with uric acid levels in the high end of the normal range have a lower incidence of Parkinson's. Whereas uric acid levels less than median value or lower end of the normal range are associated with higher incidence of Parkinson's and progression of PD [2].

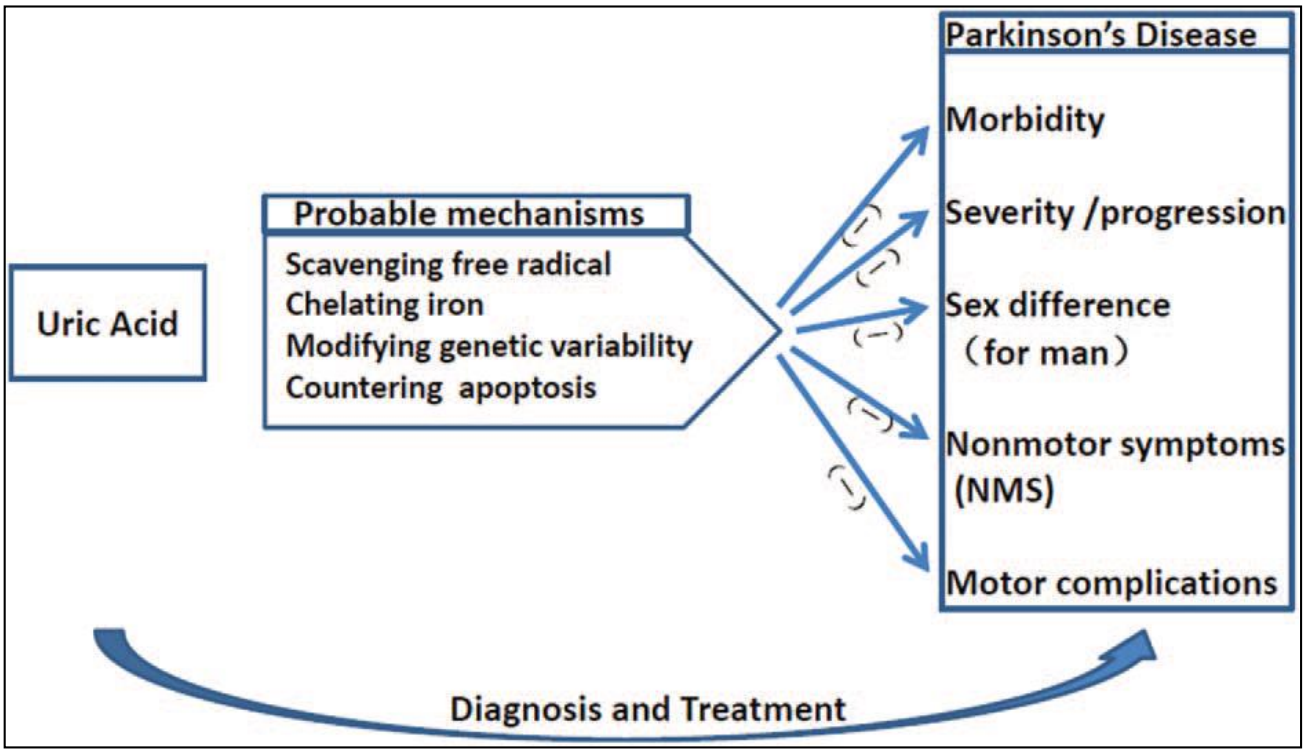

Fig 1: Probable mechanisms of uric acid in the diagnosis and treatment of Parkinson's disease [1].

1.1 Staging of Parkinson's disease

The most commonly used rating scales focus on motor symptoms. They are:

- Hoehn and Yahr stages follow a simple rating scale (introduced in 1967). Clinicians use it to describe how motor symptoms progress in PD.
- Rates symptoms on a scale of 1 to 5. On this scale, 1 and 2 represent early-stage, 2 and 3 mid-stage, and 4 and 5 advanced-stage Parkinson's.
- The Unified Parkinson's Disease Rating Scale (UPDRS) is a more comprehensive tool used to account for non-motor symptoms, including mental functioning, mood and social interaction.
- Accounts for cognitive difficulties, ability to carry out daily activities and treatment complications.

There are typical patterns of progression in Parkinson's disease that are defined in stages according to Hoehn and Yahr scale.

Stage I: During this initial stage, the person has mild symptoms that generally do not interfere with daily activities. Tremor and other movement symptoms occur on one side of the body only. Changes in posture, walking and facial expressions occur.

Stage II: Symptoms start getting worse. Tremor, rigidity and other movement symptoms affect both sides of the body. Walking problems and poor posture may be apparent. The person is still able to live alone, but daily tasks are more difficult and lengthy.

Stage III: Considered mid-stage, loss of balance and slowness of movements are hallmarks. Falls are more common. The person is still fully independent, but symptoms significantly impair activities such as dressing and eating.

Stage IV: At this point, symptoms are severe and limiting. It's possible to stand without assistance, but movement may require a walker. The person needs help with activities of daily living and is unable to live alone.

Stage V: This is the most advanced and debilitating stage. Stiffness in the legs may make it impossible to stand or walk. The person requires a wheelchair or is bedridden. Around-the-clock nursing care is required for all activities. The person may experience hallucinations and delusions [3].

Several therapies are available to delay the onset of motor symptoms and to ameliorate motor symptoms. All of these therapies are designed to increase the amount of dopamine in the brain either by replacing dopamine, mimicking dopamine, or prolonging the effect of dopamine by inhibiting its breakdown [4].

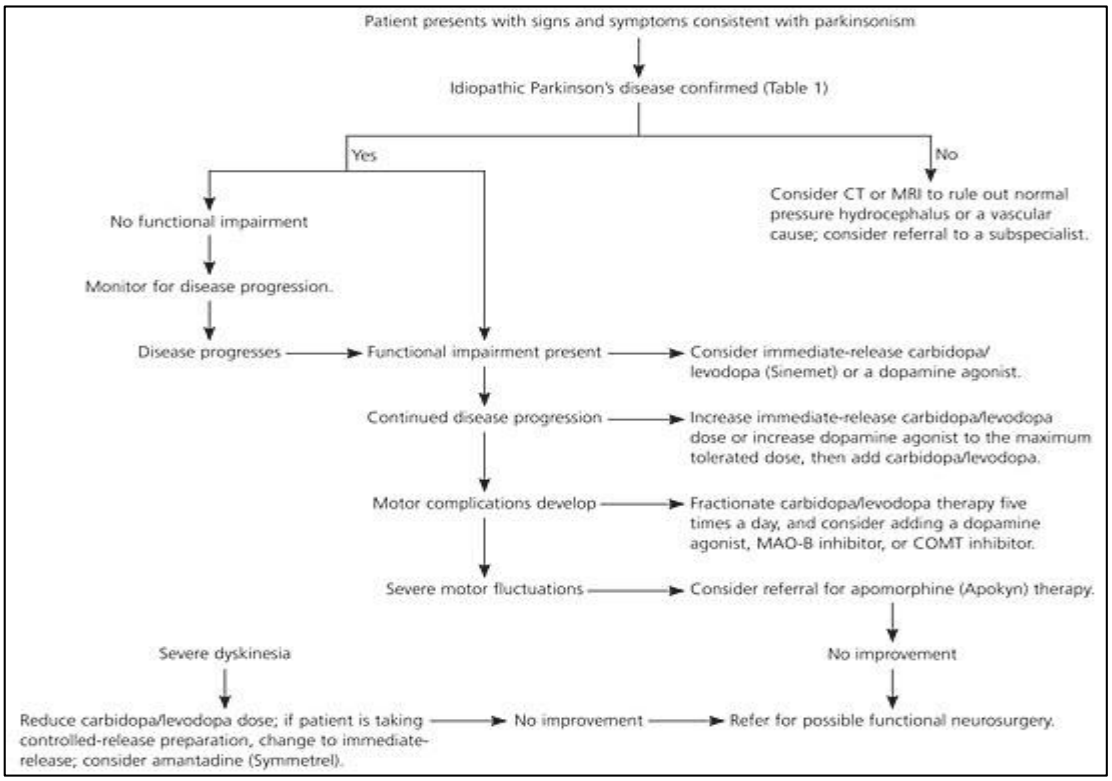

Fig 2: Algorithm for the diagnosis and management of Parkinson's disease. (CT = computed tomography; MRI = magnetic resonance imaging; MAO-B = monoamine oxidase-B; COMT= catechol *O*-methyltransferase) [5].

2. Materials and Methods

A prospective observational study was done for a period of six months at Sri Srineuro centre and Sri Vinayaka neuro centre. This study included 84 patients with PD and other comorbidities. Non cooperative PD patients were excluded from our study. Required data was collected from patient profile forms, interviewing patients and care takers. Blood samples were collected from all the participants and immediately analysed. Serum uric acid levels were determined in a clinical laboratory using standard clinical methods. We determined the correlation between serum uric acid (UA) levels and PD by using specific rating scale (H & Y stages) to categorise the patient's stage based on their symptoms.

3. Results

During the study period, a total number of 84 cases were collected, female were found to be 41 (49%) and male were found to be 43 (51%). Incidence in male is slightly more compared to female. This shows that males are more affected with Parkinson's disease. Patient's age ranged from 20 to 80 years. The mean age was found to be 69.5±9.5 years. Prevalence was observed more in 51-70 years age group. Number of patients among 61 to 70 years age group were 28 (33.3%) followed by 51 to 60 years age groups with 25 patients (29.8%).

Table 1: Distribution of cases according to risk factors

S. No	Risk factors	No. of patients	%
1.	Age(above 60)	50	59.5
2.	Family history	10	11.9
3.	Rural living	51	60.7
4.	Pesticide exposure	39	46.4
5.	Head trauma	06	7.1

Of the total number of cases collected, uric acid test was done for 60 patients. 36.6% had their serum UA levels between 3.5- 4.5 mg/dL. 64.9% patients had low uric acid level (below the median value 5.5) and 34.9% had high uric acid level.

Table 2: patients with uric acid less than median value

Gender	Number of patients
Male	20
Female	19

The patients who have undergone uric acid test are categorised into five stages using H & Y scales. Among 60 patients, the highest number of patients 21 (35%) were found in stage II and the lowest number of patients 2 (3%) are found in stage V.

Table 3: Stage wise distribution of patients (as per H & Y scale)

Stages	No. of patients	Severity
Stage 1	13	Early
Stage 2	21	
Stage 3	19	
Stage 4	5	Mid
Stage 5	2	Advanced

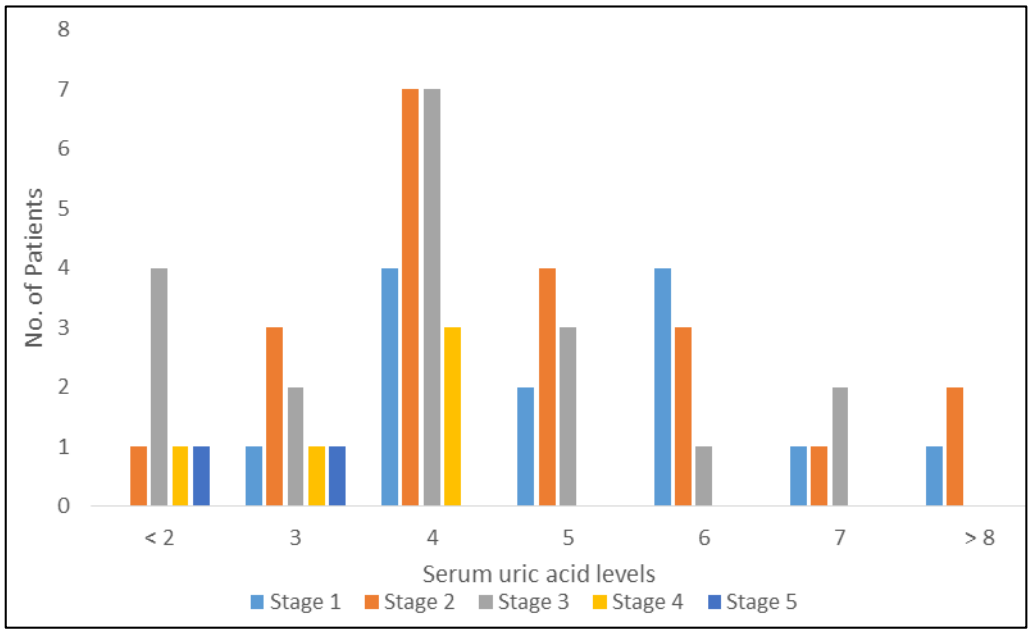

Fig 3: Distribution of patients according to their stages and uric acid levels.

The common symptoms found in our study patients are tremors (58.33%), bradykinesia (36.90%), rigidity (9.52%), masked face (Hypomimia) (4.76%), trouble sleeping (3.57%), low voice (Hypophonia) (2.38%), stooping/hunching over (2.38%), freezing (1.19%), micrographia (1.19%).

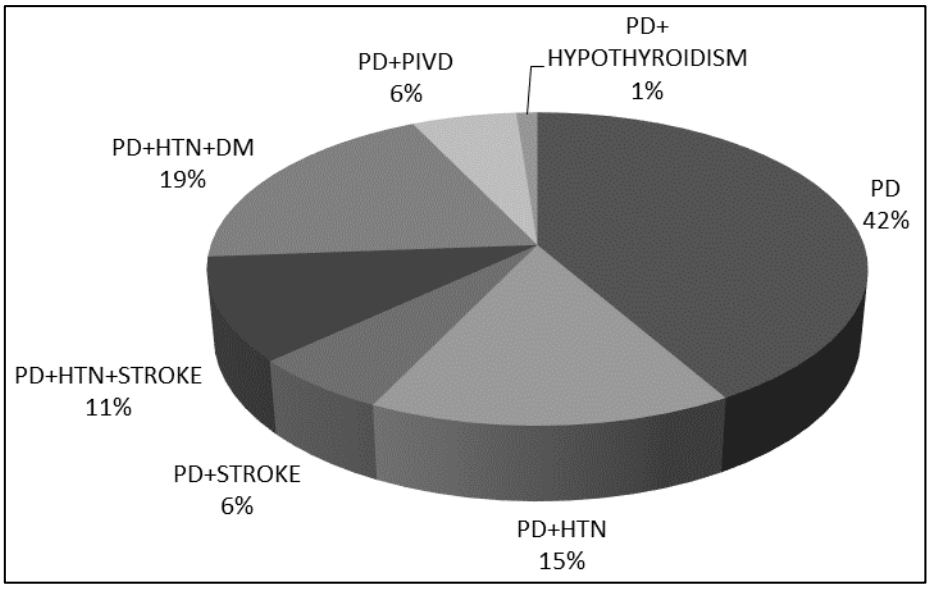

Fig 4: Showing distribution of data according to comorbid conditions.

PD-Parkinson's disease, HTN-Hypertension, PIVD-Prolapsed Intervertebral disc. The drugs that are prescribed for the treatment are Levodopa and Carbidopa (33%), Pramipexole (4%). Other drugs such as Rasagiline (26%), Trihexyphenidyl (26%), Amantadine (6%) and Entacapone (5%).

4. Discussion

In our study we found that male patients (51%) are slightly more affected than female patients (48%) and most of them were above 60 years of age which is similar to other studies. Mean age of the patients was 69.5±9.5 years. Most of the patients were among 61-70 (33.3%) years of age group. PD is a neurodegenerative brain disorder which reportedly affected up to one million people in U.S, strikes 50% more men than women, according to Florida hospital. The average age of onset is 60 years. They also identified 388 PD patients of which 202 were men and 186 were women [6]. In a study done by Farhad Iranmanesh *et al*, 2012 they found that 52% were male patients and 48% were female patients [7]. In a study conducted in Dokkyo Medical University, Japan, they identified a total of 100 patients with PD of which 46 were male, 54 were female patients of age group 68.7±8.6 years [8]. Many studies suggest that the disease is more common in men than in women. The male predominance could be due to driving or other occupations that could lead to head trauma, pesticide exposure in agriculture set up often held by men which could lead to neurodegeneration or genetic influences of x-linked genes expressed in the substantia nigra. The less prevalence of PD in women might be due to their less occupational exposure and neuroprotection from estrogen [9]. But in our study we found only slight variation of incidence among men and women, this might be due to small sample

size, rural living and equal participation of women in agricultural setup.

In our study we found that the age above 60 years (59%), rural living (60.7%) and pesticide exposure (46.4%) are the major risk factors for the incidence of PD. The other risk factors include family history (11.9%) and head trauma (7.1%). Geoparkinson study has provided an important evidence of the increased risk of Parkinson's disease in relation to exposure to pesticides [10]. Necropsy studies have found increased levels of organochlorine pesticides in the brain of patients with PD [11]. Certain chemical classes of pesticides such as organochlorines and carbamates inhibit cholinesterase enzyme, as a result of this acetylcholine levels will be increased. If acetylcholinesterase is unable to breakdown or remove acetylcholine, the muscle can continue to move uncontrollably [12]. Several synthetic pesticides have a molecular structure similar to that of MPTP. In humans, administration of the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) results in a form of Parkinsonism. The MPTP compound is converted by MAO-B to 1-methyl-4-phenyl pyridinium ion ($MPTP^+$), a potent neurotoxin in humans and animals. $MPTP^+$ is toxic to neurons by inhibiting mitochondrial complex of the electron transport chain, which results in the generation of excessive reactive oxygen species and cell death [13].

In our study majority of the patients (39 among 60 patients) had low uric acid levels i.e. lower than median value 5.5mg/dL and this association was slightly more significant in males (51%) than female (49%). A study suggests that men with uric acid levels above the median level had a 40% reduction in the incidence of idiopathic PD. The reduction in Idiopathic PD (IPD) was only marginally statistically significant [14]. Another study including 774 patients with early PD revealed that higher concentrations of urate in serum and cerebrospinal fluid (CSF) could delay PD progression and the relationship was robust in men but weak and insignificant among women [15]. In a meta-analysis done by liangshen *et al*, 2013, they found that patients with PD had lower serum levels of uric acid than controls and this association was more significant in men than women [16]. In a study conducted by Gao *et al*, 2007, they found that a higher dietary urate intake was associated with a lower risk of PD [17]. A greater than twofold reduction in risk of PD was seen among highest and lowest quantiles of dietary urate. In another study they identified 11,258 gout patients and 56,199 controls and estimated the relative risk of PD among patients with gout. They found a 30% reduction in risk of PD individuals with gout subgroup. Analysis did show that the lower rate of PD existed in both men and women [18]. In another study conducted in 2010, the serum uric acid levels in the patient group was significantly lower than the control group in both male and female patients [7]. Urate levels can be affected by diet, with a 1.0 mg/dL reduction achieved by strict avoidance of dietary purines of which meat is a major source. In addition to meat, alcohol and fructose have been demonstrated to increase blood urate levels, whereas dietary products have been found to reduce [19]. The slight difference of uric acid significance among men and women could be due to their dietary and social habits which can alter serum uric acid levels.

In our study we found significant correlation of uric acid levels and disease severity in early stage (I, II stages) and advanced stage patients, but it was not statistically significant in mid stage patients. A study reported that the level of serum uric acid decreased with increase of Hoehn and Yahr staging [20]. In an observational cohort study they found that H and Y stages were inversely associated with serum uric acid levels [21]. A recent study has found no correlation between uric acid levels and disease severity in untreated PD patients, but found that lower uric acid levels were significantly associated with lower dopamine transporter binding in the caudate, putamen and striatum [22]. The correlation of uric acid and disease severity was statistically not significant in mid stage patients and this might be due to their varied ability to take proper diet, medication adherence and gender. Increase in plasma concentrations of levodopa may cause dyskinesia, which further worsens the condition of the patient even with high uric acid levels. The reason for such insignificant data of uric acid and severity might be smoking, alcohol consumption and dairy products. Smoking can show neuroprotective action, due to this less severe symptoms may be seen even at lower uric acid levels. Alcohol have been demonstrated to increase uric acid levels [2].

In our study we found that 42% of cases were PD alone,15% of cases were PD+HTN,19% of cases were PD+HTN+DM,11% were PD+stroke+HTN,6% PD+Stroke,6% PD+PIVD and1% were PD+Hypothyroidism.

Relation between PD and Hypertension-According to research presented at the 68th Annual Meeting of the American Academy of Neurology, elevated systolic blood pressure predicts worsening motor function among patients with Parkinson's disease. Because high systolic blood pressure is a risk factor for the development of white matter hyperintensities, which in turn correlate with an increased rate of motor disability accumulation. A two -year longitudinal study of 275 participants with Parkinson's disease was conducted and they were followed for 102 weeks. They found that elevated mean systolic blood pressure was significantly associated with a greater decline in UPDRS III motor scores. High blood pressure may have a direct toxic effect on the brain that promotes the loss of neuronal integrity [23]. In our study, we found that majority of the cases with HTN as a comorbid condition are associated with moderate to severe motor symptoms.

Relation between PD and DM - Both small and large vessel atherosclerosis developed in DM might lead to vascular Parkinsonism rather than neurodegenerative PD. An alternative explanation is that there might be common genetic risk factors. Insulin resistance was detected in 50 – 80% of PD patients formally tested for glucose tolerance. A study done on abnormal protein accumulation in these diseases found that there appears to be a potential for interaction between alpha synuclein (PD) and Islet amyloid polypeptide – IAPP (diabetes), in that misfolded forms of one can induce or accelerate the formation of misfolded forms of the other [24].

Relation between PD and stroke – When the substantia nigra or the basal ganglia are affected by a stroke, this is called Vascular Parkinsonism, because it is caused by a lack of blood supply to these regions of the brain. More often than not, it takes several small strokes to produce the symptoms of Vascular Parkinsonism. Sometimes these small strokes also produce a type of dementia which is called vascular dementia. It is not unusual for people who have Vascular Parkinsonism to also have vascular dementia (Emmanuel Pinteaux *et al*). In our study we found that stroke and diabetes mellitus to a

lesser extent act as precipitating factors for Parkinson's disease.

Study site 1: In most of the cases trihexyphenidyl (anticholinergic), carbidopa/levodopa, rasagiline (MAO inhibitor) drugs were given. 70% improvement of symptoms was observed. The dose of levodopa/carbidopa is fractionated according to severity of disease condition. In cases such as early PD only trihexyphenidyl was given. Based on severity of disease and levodopa/carbidopa induced dyskinesia amantadine (NMDA receptor blocker) was given. COMT inhibitors (ex: entacapone) and dopamine agonists (ex: pramipexole) are not much prescribed in this study site.

Study site 2: A combination of levodopa + carbidopa+ entacapone (COMT inhibitor) are mostly prescribed in this study site. In few cases pramipexole (dopamine agonist) or trihexyphenidyl) are given along with the above combination.
According to American academy of family physicians 2018, if functional impairment is seen in patients immediate release carbidopa/levodopa or a dopamine agonist is considered. In case of disease progression, the dose of immediate release carbidopa/levodopa is increased or dopamine agonist dose is increased to the maximum. If motor complications are developed, fractionated carbidopa/levodopa therapy five times a day is recommended along with addition of dopamine agonist, MAO inhibitor or COMT inhibitor. In case of severe motor fluctuations, apomorphine a nonselective dopamine agonist therapy is considered. In case of severe dyskinesia, amantadine and reduction of carbidopa/levodopa dose is recommended. If patient is taking controlled release preparation, it must be changed to immediate release. In a study conducted by Pratibha Surathi *et al*, 2017 [25], levodopa and trihexyphenidyl were most commonly prescribed. A higher use of trihexyphenidyl could be due to its easy availability, low cost, and better tolerability in their patients, who were relatively young at the time of onset of their disease.

4.1 Role of clinical pharmacist

Pharmacist should play a vital role in early detection of PD and also identify the risk factors involved in the occurrence and progression of PD in individual patient in order to provide effective drug therapy. In some cases administration of levodopa for long period of time may induce dyskinesia which might get confused with disease severity and could lead to further increase in the dose of levodopa/carbidopa which further worsens the patient condition. Pharmacist should identify whether the dyskinesia occurred in the patient is drug induced or disease related. This could help physician to provide fractionised dose of levodopa/carbidopa to individual patient and prevent occurrence of adverse drug reactions.
Pharmacist should also play a major role in counselling the patient regarding importance of medication adherence, diet that includes antioxidant rich foods.

5. Conclusion

Most of the patients had low uric acid levels i,e lower than median below 5.5 mg/dL and this association was slightly more significant in male than female. Significant correlation was found between uric acid levels and disease severity in early and advanced stages, but it is not statistically significant in mid stage patients. Thus, uric acid could be considered as a biomarker and prognostic tool for PD. Comorbid conditions such as hypertension may be associated with a moderate to severe decline in motor functions in majority of the patients and conditions such as DM and Stroke may act as precipitating factors for PD to a lesser extent. Majority of the patients were treated with Trihexyphenidyl, Carbidopa & Levodopa, Rasagiline. Clinical Pharmacist could play a crucial role in assessing the correlation of uric acid with progression of disease thereby suggesting necessary treatment alterations and dietary modifications which could enhance antioxidant properties and reduction in the progression of disease.

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