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Association of Serum Uric Acid with Parkinson Disease

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Abstract:

Background: *Several studies have identified that low serum uric acid (UA) is a possible risk factor for Parkinson Disease (PD). The aim of my study was based on evaluation of association of serum uric acid with Parkinson Disease (PD).* ***Objective:*** *To evaluate the association of serum uric acid with Parkinson Disease(PD).* ***Methodology:*** *It was a case control study carried out in the Department of Neurology of Bangabandhu Sheikh Mujib Medical University. A total 50 patients of PD aged 45 years or above were taken as cases; and age and sex matched 50 healthy subjects or patients other than PD were taken as control. Serum UA levels were measured in both groups. Besides, any association was searched between serum UA with age, sex, duration and stage of PD, BMI and dietary habit.* ***Results:*** *The mean serum uric acid level in case group was 4.25±1.00 mg/dl and that of control group was 4.73±1.29 mg/dl. The mean serum uric acid in case group was statistically significant (p=0.038 which was <0.05) lower than that of control group. Serum UA levels gradually diminished as Hoehn & Yahr stage of PD increased. Also, disease duration of PD was found inversely related with serum UA. Male subjects in both case and control group had higher serum UA level than their female counter-part, but they had statistically significant higher UA in control group. In this study no correlation was found between age and BMI with serum UA in both case and control. Any association between serum UA and dietary habit was not found in this study because maximum subjects of this study used to take average protein diet.* ***Conclusion:*** *The aim of the study was to explore the association between serum uric acid with Parkinson Disease. The present study found statistically significant association between low serum uric acid with Parkinson Disease.*

Keywords: *Serum uric acid (UA) and Parkinson Disease (PD).*

Introduction:

Parkinson disease (PD) is a degenerative disease, which involves dopaminergic neuron of substantia nigra. The number of dopaminergic neuron is reduced to 30% or less in PD patient. It begins between 45 and 70 years of age with peak age of onset in the sixth decade. A tetrad of hypokinesia and bradykinesia, resting tremor, postural instability and rigidity are the core features of PD[1].

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The overall age- and gender-adjusted prevalence rate is 360 per 100,000 and incidence rate is 18 per 100,000 per year[2].

Prevalence is higher among males (19.0 per 100,000) than females (9.9 per 100,000)[3].

A diagnosis of PD can be made in patients who present with bradykinesia and at least two of the three cardinal signs- resting tremor, rigidity and postural instability. PD accounts for 75% of all cases of parkinsonism, the remaining cases result from other neurodegenerative disorder, cerebrovascular disease and drugs. Familial forms of known autosomal dominant and recessive form of PD comprise 5% of cases of PD[4].

Oxidative stress in the brain has been implicated as playing role in the onset of PD and leads to an increase in oxidative damage in the substantia nigra, manifested as lipid peroxidation, protein oxidation and DNA oxidation[5]. Such damage is probably mediated through toxic action of nitric oxide (NO) that is involved in formation of oxidizing species such as peroxynitrite and is accumulated over time possibly contributing to nigral cell death[5,6,7].

PD patients are found to have decreased antioxidant defence of cells that render them susceptible to damage from reactive oxygen species (ROS) and nitrogen species (RNOS) and others formed during cell metabolism and oxidative stress[8,9].

Uric acid is known to be an important natural antioxidant in blood and brain tissue scavenging superoxide, peroxynitrite and hydroxyl radical[7]. It has been shown to inhibit free radical-initiated lipid peroxidation and DNA damage[10]. In addition, it forms strong complexes with iron particularly ferric form[11] which may contribute to oxidative damage in PD by promoting the formation of highly reactive hydroxyl free radical[12]. Moreover, uric acid has been shown to slow dopamine (DA) auto-oxidation rate in caudate nucleus and substantia nigra homogenates of parkinsonian patients[13]. Any loss of this purine metabolite could result in a diminished free anti-oxidant capacity. The decrease level of uric acid observed in nigrostriatal human dopamine neurons[13] may contribute to an environment susceptible to oxidative stress and prevention of dopaminergic cell death in animal models of PD with the administration of UA[14]. Since DA oxidation and the consequent generation of reactive oxygen species may contribute to the degeneration of dopaminergic neurons, UA may play an important protective role.

Higher serum uric acid levels have been associated with a significantly reduced risk of PD, with evidence of a dose effect relationship implying that reduced uric acid may have a causal role in PD[15-21]. Moreover, lower plasma uric acid levels were found in treated PD patients compared to healthy controls[22].

In addition, about untreated patients with early PD, higher plasma uric acid concentrations were associated with a slower rate of clinical progression[23].

Several of these studies include only men[15,17,19]. Conflicting results concerning the association of low serum UA levels with either the risk or the progression of PD have been reported in these studies comprising both males and females[16,18,20-23]. Some report states that this correlation is significant only for men[18,21,23] whereas others did not find any gender differentiation[16,18,22].

The aim of the present study was to investigate serum uric acid levels in PD patients and control subjects; and compare with each other to find any association of serum uric acid with PD.

Methods:

This was a case control study. This study took place in the department of Neurology at Bangabandhu Sheikh Mujib Medical University, Dhaka which was conducted from 1st January 2010 to 31st December 2011 for the duration of two years. The target population for this study included all patients presented with Parkinson disease of age between 45 years and above; and of both sexes. Age and sex matched normal people or patients other than Parkinson disease were the controls.

A total number of 50 patients presented with Parkinson disease were enrolled in this study. Informed written consent was taken from each patient or his/ her attendant. All information regarding history, physical findings and other risk factors for PD were collected to fill the predesigned

questionnaire. Relevant physical examinations like nervous system examination, selected general and systemic examination were recorded.

Results and Observations:

Total 100 subjects were enrolled in this study among them 50 were PD patients comprising the case group and 50 healthy subjects on non-PD patients comprising the control group. The findings of the study are presented here.

Table-I

Age distribution of the study population (n=100)

Age (in year)	Group I (n=50)		Group II (n=50)		P value
	N	%	n	%	
45-50	16	32.0	13	26.0	
51-60	17	34.0	19	38.0	
61-70	11	22.0	16	32.0	
>70	6	12.0	2	4.0	
Mean±SD	58.48±10.63		58.36±8.91		0.951^{ns}
Range (min-max)	(30-87)		(45-80)		

NS=Not significant. P value reached from unpaired t-test.

Group I: Patient with Parkinson Disease (PD); Group II: Control subject.

A total of 100 subjects were included in the study. They were divided into four groups according to age. Majority of the patients were found in the age group 51-60 years, in which 17(34.0%) patients in group I and 19(38.0%) subjects in group II. The mean age was found 58.48±10.63 years in group I and 58.36 ± 8.91 years in group II. The value of unpaired t-test was 0.951 and it was not statistically significant (p>0.05).

Table-II

Sex distribution of the study population (n=100)

Sex	Group I (n=50)		Group II (n=50)		P value
	N	%	n	%	
Male	39	78.0	32	64.0	0.122^{ns}
Female	11	22.0	18	36.0	

P value reached from chi square test.

Table II shows, in group I, 39 (78.0%) patients were male and 11 (22.0%) patients were female. In group II, 32 (64.0%) subjects were male and 18 (36.0%) subjects were female. There was no significant (p>0.05) difference was found between two groups regarding sex distribution. Male female ratio was 2.4:1

Table-III

Distribution of mean serum uric acid level according to male and female sex of the study population (n=100)

	Group I (n=50) Mean±SD	Group II (n=50) Mean±SD
Male	4.38±0.98	5.13±1.23
Female	3.77±0.94	4.36±1.27
P value	0.075^{ns}	0.034^{s}

NS=Not significant, S= significant,
P value reached from unpaired t-test.

In group I patients, the mean s. uric acid level was 4.38±0.98 mg/dl and 3.77±0.94 mg/dl in male and female respectively. In group II subjects the mean s. uric acid level was 5.13±1.23 mg/dl in male and 4.36±1.27 mg/dl in female. The mean s. uric acid level was higher in male subjects but not significant in group I, whereas it was significantly higher in male subjects in group II (Table III).

Table-IV

Distribution of the study population according to personal history (n=100)

Personal history	Group I (n=50)		Group II (n=50)		P value
	N	%	n	%	
Smoking					
Present	20	40.0	16	32.0	0.404^{ns}
Absent	30	60.0	34	68.0	
HTN					
Present	15	30.0	24	48.0	0.065^{ns}
Absent	35	70.0	26	52.0	
Socioeconomic status*					
Low	9	18.0	1	2.0	
Middle	40	80.0	42	84.0	0.004^{s}
High	1	2.0	7	14.0	
Dietary habit**					
Average protein diet	44	88.0	49	98.0	0.055^{ns}
Low protein diet	6	12.0	1	2.0	

S=Significant
NS=Not significant
P value reached from chi square test.

The above table shows the personal history of study patients. Smoking was 20(40.0%) in group I and

16(32.0%) in group II. HTN was found 15(30.0%) patients in group I and 24(48.0%) subjects in group II. Low socioeconomic status was found 9(18.0%) in group I and 1(2.0%) in group II. Middle socioeconomic status was 40(80.0%) in group I and 42(84.0%) in group II. High socioeconomic status was found 1(2.0%) in group I and 7(14.0%) in group II. In dietary habit, average protein diet was found 44(88.0%) in group I and 49(98.0%) in group II. Low protein diet was found 6(12.0%) in group I and 1 (2.0%) in group II. Only socioeconomic status was statistically significant ($p<0.05$) but others were not statistically significant ($p>0.05$) between two groups in chi square test.

*Socioeconomic status based on monthly income
Low: Tk< 15000.
Middle: Tk 15000- 40000.
High: Tk> 40000.

Reference : State of children of the world 2007, UNICEF.

**Dietary habit
Average protein diet:
65- 70%: Carbohydrate.
15- 20%: Protein.
10- 15%: Fat.

Reference: Preliminary Report on Household Income and Expenditure Survey- 2010, Bangladesh Bureau of Statistics.

Table-V

Distribution of the study population according to body mass index (n=100)

BMI (kg/m^2)	Group I (n=50)		Group II (n=50)		P value
	N	%	n	%	
Under weight (<18.5)	0	0.0	0	0.0	
Normal weight (18.5-24.9)	48	96.0	50	100.0	
Over weight (25-29.9)	2	4.0	0	0.0	
Obesity (>30)	0	0.0	0	0.0	
Mean±SD Range (Min-Max)	22.61±1.3 (20-35)		22.34±1.17 (19-24)		0.277^{ns}

NS=Not significant
P value reached from unpaired t-test.

Table IV shows the mean (± SD) BMI was 22.61±1.3 kg/m^2 in group I and 22.34±1.17 kg/m^2 in group II. The mean BMI was not statistically significant ($p>0.05$) between the two groups.

Table-VI

Distribution of the study population according to serum uric acid level and serum creatinine level (n=100).

Investigations	Group I (n=50) Mean±SD	Group II (n=50) Mean±SD	P value
Serum uric acid (mg/dl)	4.25±1.00	4.73±1.29	0.038^{s}
Range (min-max)	(2.3-5.8)	(2.2-7.2)	
S. Creatinine (mg/dl)	1.08±0.29	1.03±0.46	0.447^{ns}
Range (min-max)	(0.3-2.2)	(0.5-2.9)	

NS=Not significant, s=significant
P value reached from unpaired t-test.

Table VI shows the investigations of the study patients. The mean serum uric acid 4.25±1.00 mg/dl with range from 2.3 to 5.8 mg/dl in group I and 4.7.3±1.29 mg/dl with range 2.2 to 7.2 mg/dl in group II. The mean s. creatinine 1.08±0.29 mg/dl with range 0.3 to 2.2 mg/dl in group I and 1.03±0.46 mg/dl with range from 0.5 to 2.9 mg/dl in group II. The mean serum uric acid level was statistically significant ($p<0.05$) between the two groups but S. creatinine level was not statistically significant ($p>0.05$) between the two groups in unpaired t-test.

Table-VII

Distribution of mean serum uric acid level of the study population according to dietary habit (n=100)

Dietary habit	Group I (n=50) Mean±SD	Group II (n=50) Mean±SD	P value
Average protein diet	4.23±0.97	4.69±1.27	0.057^{ns}
Low protein diet	4.35±1.3	7.0-	-

NS=Not significant
P value reached from unpaired t-test.

Patients who received average protein diet, the mean s. uric acid level was 4.23±0.97 mg/dl and 4.69±1.27 mg/dl in group I and group II respectively. Patients who received low protein diet the mean s. uric acid level was 4.35±1.3 mg/dl in group I, however in group II, only one patient received low protein

diet and his s. uric acid level was 7.0 mg/dl. The mean s. uric acid level was not significant (p>0.05) in both groups in unpaired t-test.

Table-VIII

Distribution of the study patients according to stages of Parkinson disease (n=100)

Stages of Parkinson disease	Number of patients	Percentage
Stage I	26	52.0
Stage II	12	24.0
Stage III	9	18.0
Stage IV	1	2.0
Stage V	2	4.0
Mean±SD	1.82±1.06	
Range (min-max)	(1-5)	

Stage I: Unilateral disease

Stage II: Bilateral disease

Stage III: Bilateral disease with postural instability

Stage IV: Severe disability, patient still able to stand or walk unaided

Stage V: Wheelchair bound or bed ridden unless aided

The above table shows the stages of Parkinson disease of the study patients. The mean stages of Parkinson disease was found 1.82±1.06 with range from 1 to 5 in patients having PD.

Table-IX

Distribution of mean serum uric acid level in case group (Group I) according to disease duration.

Serum uric acid level (mg/dl) Disease duration (in years)	Mean±SD
1-4	4.27±0.95
5-8	4.08±0.42

Table-X

Distribution of mean serum uric acid level in case group (Group I) according to stage of PD.

Stage of PD	Serum uric acid level (mg/dl) Mean ± SD
I	4.70±0.87
II	4.19±1.02
III	3.70±1.27
IV	*4.80±0.00
V	2.50± 0.14

*Only one patient in stage I in case group

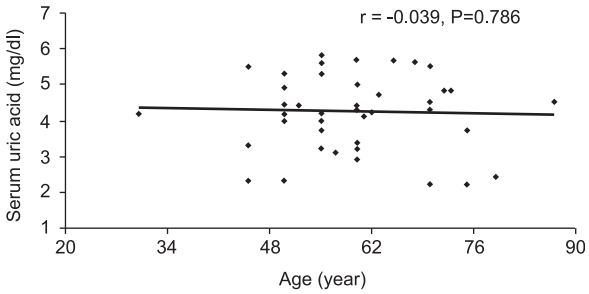

Fig.-1: *Scatter diagram showing no correlation (r = -0.039; p=0.786) between age with serum uric acid level (mg/dl) in patients having Parkinson disease.*

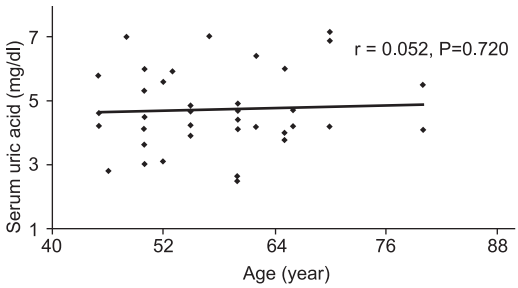

Fig.-2: *Scatter diagram showing no correlation (r=0.052; p=0.720) between age with serum uric acid level (mg/dl) in healthy control subject.*

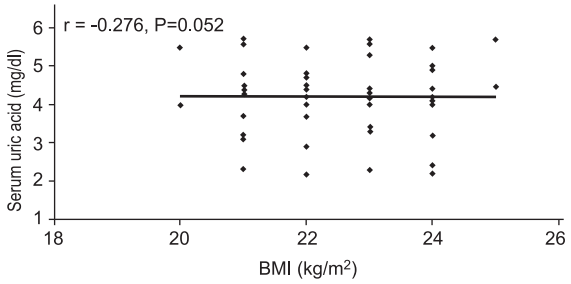

Fig.-3: *Scatter diagram showing no correlation (r = -0.276; p=0.052) between BMI with serum uric acid level (mg/dl) in patients having Parkinson disease.*

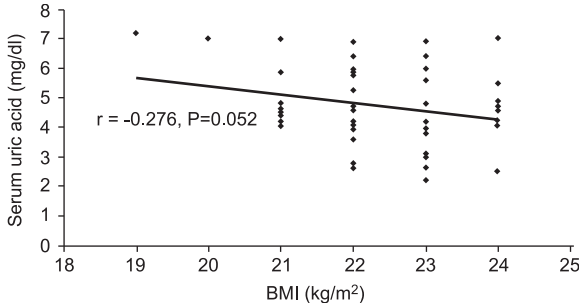

Fig.-4: *Scatter diagram showing no correlation (r = -0.253; p=0.076) between BMI with serum uric acid level (mg/dl) in healthy control subject.*

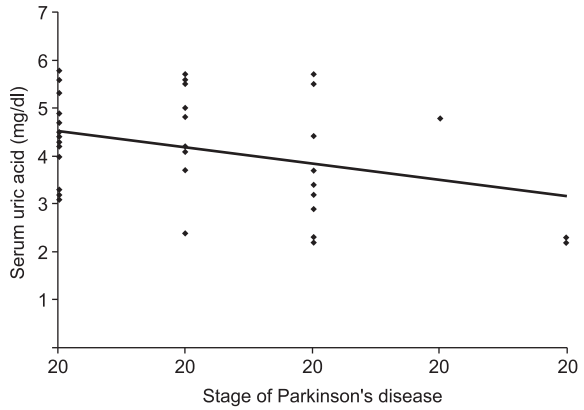

Fig.-5: *Scatter diagram showing significant negative correlation (r=-0.359; p=0.01) between stage of Parkinson disease with serum uric acid level (mg/dl) in patients having Parkinson disease.*

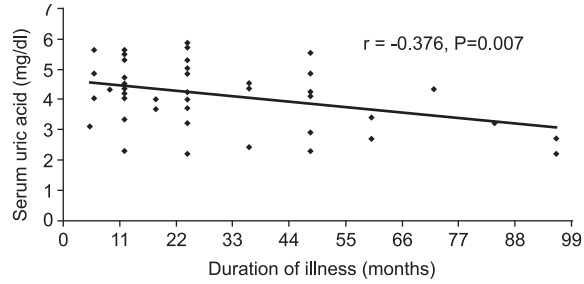

Fig.-6: *Scatter diagram showing significant negative correlation (r= -0.376; p=0.007) between duration of illness with serum uric acid level (mg/dl) in patients having Parkinson disease.*

Discussion:

This case control study was carried out with an aim to explore the association between serum uric acid level with patients of PD. For this purpose, a total 50 patients of PD age ranging from 45 years or above were purposively selected who attended in the Department of Neurology of Bangabandhu Sheikh Mujib Medical University, Dhaka and 50 healthy and non-PD subjects were taken as control during January, 2010 to December, 2011.

In the present study, patients and controls did not differ significantly from each other with respect to age. The mean age was found 58.48±10.63 years in group I (patient group) and 58.36±8.91 years in group II (control group). The value of unpaired t-test was 0.951 and it was not statistically significant (p >0.05). The results were in accordance with the study[24]. Parkinson disease usually occurs at the age of 45 years or over. In this study in group I 39 (78%) patients were male and 11 (22%) patients were female. In group II 32 (64%) subjects were male and 18 (36%) were female. There was no significant difference between two groups (p>0.05) regarding sex distribution (Table-II). These results were in accordance with the study of Andreadou et al[24].

The current study showed that serum uric acid level was 4.38±0.98 mg/dl and 3.77±0.94 mg/dl in male and female respectively in group I. In group II the mean serum uric acid level was 5.13±1.23 mg/dl in male and 4.36±1.27 mg/dl in female. The mean serum uric acid level was higher in male subjects which was not significant (p=0.075; p>0.05) in group I but it was significantly higher in male in group II (p=0.034; p<0.05). In Andreadou et al 2009 study[24] showed males had statistically significant higher serum uric acid than their female counterparts in both case and control groups. The results of the present study were also similar to that of study done by Andreadou et al.[24] except for statistically insignificant higher serum uric acid in male patients in case group. This might be due to small number of female patients in group I which might not represent actual serum uric acid level of female PD patients (Table III).

In the present study, among group I patients 20 (40%) were smoker and 30 (60%) were non-smoker. Among group II subjects, 16 (32%) were smoker and 34 (68%) were non-smoker. Smoking was not statistically significant between the two groups; (p>0.05). These results were in contradiction with that of Weisskopf study[17] which showed pack-years of smoking was associated with increasing serum uric acid concentration, indirectly suggesting decreased incidence of PD. This discrepancy might be due to increased number of female patients in control group who were non-smoker (Table IV).

About hypertension, in this study, in group I, 15 (30%) were hypertensive and 30 (60%) were non-hypertensive. In group II, 24 (48%) subjects were hypertensive and 26 (52%) were non-hypertensive. Hypertension was not statistically significant

between two groups, as p value was 0.065 which was greater than 0.05. These results were consistent with that of Weisskopf et al. study[24] which showed hypertension was not statistically associated with PD (Table- IV).

Regarding socioeconomic status, low socioeconomic status was found in 9 (18%) patients of group I and 1 (2%) in group II; middle status was found in 40 (80%) in patients in group I and 42 (84%) subjects in group II; high socioeconomic status was found in 1 (2%) in group I and 7 subjects (14%) in group II. Low socioeconomic status was significantly associated with PD on statistical point of view (p=0.004) (Table IV).

About the dietary habit, in this study, among group I patients, 44 (88%) took average protein diet and 6 (12%) took low protein diet. In group II, 49 (98%) took average protein diet and 1 patient (2%) took low protein diet. Dietary habit was not statistically significant (p>0.05) between the two groups. These results were to some extent similar to that of Gao X et al. study[19] which showed increased serving of meat per day associated with reduced occurrence of PD. (Table IV)

In the current study, in group I patients mean BMI (±SD) was 22.61±1.3 kg/m² and in group II 22.34±1.17 kg/m². The mean BMI was not statistically significant (p=0.277) between the two groups. These results were different from that of Annamaki T et al.[22] which showed mean BMI in case group was 25.1±3.4 kg/m² and in control group was 26.8±3.6 kg/m²; p value was marginally significant (p=0.05). This discordance may be because of the patient presenting in BSMMU neurology department did not represent whole of the population of PD and patients from remote and rural areas did not usually come to BSMMU. (Table V)

The present study showed that mean serum uric acid level in group I patients was 4.25±1 mg/dl and in group II subjects it was 4.73±1.29 mg/dl. Mean serum uric acid level was significantly elevated in group II on statistical point of view: p=0.038. These results (Table VII) are similar to that of several studies [24,22,19,15,17].

The mean serum creatinine in group I patients was 1.08±0.29 mg/dl and in group II subjects was 1.03±0.46 mg/dl. It was not statistically significant between the two groups (p= 0.447). It was tried deliberately so that both patient and control group to have normal renal function, thereby tried to exclude renal function as a confounding variable of serum uric acid level. (Table VI)

In the present study subjects who received average protein diet the mean serum uric acid level was 4.23±0.97 mg/dl in group I and 4.69±1.27 mg/dl in group II. Subjects who received low protein diet, the mean serum uric acid was 4.35±1.3 mg/dl in group I and only one patient in group II and his serum uric acid level was 7 mg/dl. The mean serum uric acid level was not significant between the two groups. In our country, people are used to take average protein diet. In the current study, both in case and control group, subjects who mainly took average protein diet were included, thereby it was tried to obviate the role of dietary habit over the level of serum uric acid. In the study of Garj JP et al.[25], it was shown that increase total meat intake was associated with raised level of serum uric acid. (Table VII)

In the current study there was no correlation between age of patients of group I with their serum uric acid level (r= -0.039; p= 0.786) and similarly in group II subjects (r= 0.052; p=0.720). These results were in accordance with that of Andreadou et al [24] studies where age did not affect the level of serum uric acid in both case and control groups. (Figure 1, 2)

In the study of de lau LM et al 2005[16], there was a positive association between BMI of subjects and their serum uric acid level. In the present study, there was no correlation between BMI of patients with their serum uric acid level (r= - 0.276; p= 0.052) in group I and similarly in group II (r= -0.253; p= 0.076). These results were in accordance with that of Andreadou et al[24] which showed no significant association between serum uric acid level and BMI in both patient and control groups. (Figure 3, 4)

In the present study the distribution of study patients according to stages of PD were as follows – Stage I 26 (52%), Stage II 12 (24%), Stage III 9 (18%), Stage IV 1 (2%) and Stage V 2 (4%). The serum uric acid level progressively decreased as the stage of PD increased in the present study (r= -0.359 ; p= 0.01). These results (Table VIII, Fig.-5) were similar to that of several studies[24,23].

The duration of illness had a significant negative correlation with serum uric acid level in case group in this study (r=-0.376 ; p=o.oo7). These results were in agreement with those of some other studies[24,23] which showed increasing duration of PD were associated with progressively reduced level of serum uric acid level (r= -0.0397 ; p= 0.009). (Figure 6)

In the recent study of Chen et al 2009[21], the inverse association of serum UA with the risk of developing PD was significant only for men, a finding that was attributed to the small sample size. In contrast to the study of others[16,18, 20-22] did not find any gender differences regarding the risk of PD. Since low serum UA levels were found in the CSF and substantia nigra of PD patients, low serum UA level in PD patients may reflect low intracellular UA concentration in brain tissue.

UA may prevent the degradation of superoxide dismutase and consequently may assist in the removal of superoxide that reacts with nitric oxide to produce peroxynitrite and ultimately hydroxyl radical[7]. Further more it was found to be effective at preventing peroxynitrite from nitrating the tyrosine residues of protein[7,26]. Indeed an increased accumulation of 3- nitrotyrosine (a marker of peroxynitrite formation) was observed in Gord PF et al study[27]. Moreover, UA was found to undergo antioxidant reaction with DNA radicals and to induce fast chemical repair of oxidative damage on DNA that results from the toxic action of NO/ peroxynitrite[28]. In addition, it might protect cells through an astroglia mediated mechanism[29].

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