

Association between serum biochemical levels, related to bone metabolism and Parkinson's disease

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Background: Vitamin D insufficiency and serum calcium disturbance have been reported to be more common in Parkinson's disease (PD) patients than in healthy control subjects, which may be due to a chronic disease or reduced mobility contributes to these relatively disturbances. Because of the high-vitamin D insufficiency in our population, we aimed to compare a biochemical levels which are related to bone metabolism, in PD patients in comparison with age-matched healthy controls, for the 1st time in a Middle East population. **Materials and Methods:** This case-control study was involved 105 (20 were excluded) PD patients, who were age- and -sex matched with 112 controls. 25-hydroxyvitamin D (25OHD) and parathyroid hormone analyzed by enzyme immunoassay; another laboratory data including, calcium, phosphorous, and alkaline phosphatase were performed by spectrophotometric methods. **Results:** There was no significant difference in 25OHD between PD patients and control group ($P = 0.071$). 25OHD level was not significantly different in PD patients compared to controls {odds ratio 1.003, (confidence interval [CI], 0.98-1.02), P value 0.793}. None of the other biochemical levels did not induce more chance for PD, only we observed in men has more risk of PD than women (odds ratio 2.53, [CI, 1.27-5.03], P value 0.008). **Conclusion:** Our data do not support a possible role of vitamin D insufficiency in PD. Regarding to variable changes in biochemical markers in PD patients than in controls; further studies are suggested to determine any plausibility role of them as a causal relationship or as an outcome of PD.

Key words: Bone metabolism, 25-hydroxyvitamin D, Parkinson's disease, serum calcium

INTRODUCTION

Parkinson's disease (PD), a major cause of disability in elderly individuals, is a movement disorder leading to immobility and frequent drops that results from the selective loss of dopaminergic neurons in the substantia nigra of the brain.^[1] Although, the main causes of PD is relatively unknown but many environmental risk- factors for PD have been proposed such as oxidative stress, inflammation, mitochondrial dysfunction,^[2-4] various food groups and specific micro elements such as calcium and vitamin D.^[5]

Role of calcium in PD explained by rising in intracellular calcium concentrations, which represents one of the final events leading to nerve cell death.^[6] There is one hypothesis that the primary factor driving neurodegenerative changes in PD is the metabolic stress created by ionized calcium entry, particularly in the face of genetic or environmental factors that compromise oxidative defenses or proteostatic competence.^[7]

Related to the role of biochemical markers, many studies have been shown this relatively correlation in PD patients.^[8-10] Abou-Raya *et al.* reported that diminished level of serum calcium and alkaline phosphatase (ALP) of PD patients in comparison with healthy control group and have been suggested that this is due to inactivity, reducing sun exposure and calcium and vitamin D consumption in these patients,^[8] while the other study showed increased serum level of calcium significantly more than control group.^[9]

In addition, high prevalence of hypovitaminosis D has been reported in PD patients with later stage of PD.^[11-14] Animal and human data support the idea that vitamin D deficiency perhaps involved in the pathogenesis, progression, and clinical manifestations of PD^[15] also a significant decreasing in vitamin levels in patients with PD compared with matched healthy control subjects and patients with Alzheimer disease has been displayed.^[12]

Beside of these doubtful evidences about the role of biochemical levels related to bone metabolism on PD and

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also there are no reports on this correlation focus in Middle East, in this case-control study, we aimed to determine associations circulating 25-hydroxyvitamin D (25OHD), Ca, ALP, Parathyroid hormone (PTH), and phosphorus levels of patients with PD, in comparison with healthy individuals in Iranian samples.

MATERIALS AND METHODS

Study design

In a case-control study 125 consecutive patients with PD diagnosed by expert neurologists from the out-patient and clinical wards of the Alzahra Hospital in Isfahan, Iran. Patients were examined from September to November 2011 (fall season in Iran). Patients with familial or early onset of PD (<40 years old) or if they were already taking vitamin D supplements or 1, 25 vitamin D or any medications that might interfere with vitamin D and bone metabolism were ineligible for this study. Finally, 105 patients with PD were eligible to participate in the study.

The control participants had no history of neurologic disease (by examination where available and by self-report for all others). The recruitment of cases and control groups ($n = 112$) were taken place at approximately the same time.

The diagnosis of PD was based on diagnostic criteria for PD, including existence of resting tremor, bradykinesia and/or muscle rigidity.^[15] All patients provided written informed consent. The study protocol was reviewed and approved by the ethics in Research Committee, Isfahan University of Medical Science.

Biochemical analysis

Serum 25OHD concentration was defined as deficient when less than 20.0 ng/mL and insufficient when less than 30.0 ng/mL.^[16,17] 25OHD and PTH (normal range: 10-65 IU/L) were analyzed by enzyme immunoassay (Biomerica, CA and IDS, UK). Laboratory data of peripheral blood including calcium (normal range: 8.2-10.6 mg/dL), phosphorous (normal range: 2.5-4.5 mg/dL) and ALP (normal range: 64-306 mg/dL) were performed by spectrophotometric methods (Hitachi 902 auto analyzer). In each case, serum samples were obtained on the visit day, after an overnight fast in acid washed glass tubes. Serum was separated, as soon as possible and stored at -20° .

Statistical analysis

Standard statistical methods (mean, SD) were utilized to summarize parametric values and *t*-test and K-square were employed to compare the control group versus group of patients affected by PD.

Associations between PD and biochemical such as 25OHD, PTH, ALP were estimated using logistic regression models controlling for age and sex.

The data were analyzed using SPSS 16.0 statistical package (SPSS Inc.). *P* value ≤ 0.05 was regarded as significant.

RESULTS

The study included 105 patients with PD, and 112 healthy controls. As shown in Table 1, Serum calcium and phosphorus was lower in PD patients compared with controls (mean \pm SD, $[9.27 \pm 0.04]$ versus $[9.90 \pm 0.63]$ ($P = 0.36$) and phosphorus $[3.38 \pm 0.02]$ versus $[3.57 \pm 0.05]$ ($P = 0.003$), respectively) but due to lack of enough frequency of hypo- and hypercalcemia and phosphatemia, it was not applicable *P* value for the suggestion. In the patients, 25OHD serum level was in high range of deficient levels (<20 ng/mL)^[16,17] in PD patients and control group (45.7% and 60.7%, respectively) but there was no significant difference in 25OHD between PD patients and controls (odds ratio 1.003, [CI, 0.98-1.02], *P* value 0.793) [Table 2]. In logistic regression model after adjustment for age and sex, in PD patients, none of the biochemical levels did not induce more chance for PD, only we observed in men has more risk of disease than women (odds ratio 2.53, [CI, 1.27-5.03], *P* value =0.793, *P* value =0.008).

DISCUSSION

The results of the present study demonstrated that patients with PD had not significantly lower serum calcium and 25OHD level but significantly lower serum of phosphorous

Table 1: Serum biochemical markers in the study population

Variables	PD	Control	<i>P</i> value
Age (mean \pm SD)	61.49 \pm 1.1	64.52 \pm 13.3	0.06
Sex (%)			
Male	84 (67.2)	71 (48.0)	0.001
Female	41 (32.8)	77 (52.0)	
25OHD (ng/mL) (%)			
Normal	57 (54.3)	44 (39.3)	0.071
Hypo	48 (45.7)	68 (60.7)	
Calcium (mg/dL) (%)			
Normal	116 (92.8)	145 (98.6)	Not applicable
Hypo	9 (7.2)	0	
Hyper	0	2 (1.4)	
Phosphorus (mg/dL) (%)			
Normal	125 (100)	142 (96.6)	Not applicable
Hypo	0	1 (0.7)	
Hyper	0	4 (2.7)	
PTH (ng/mL) (%)			
Normal	48 (47)	52 (46.4)	0.351
Hyper	54 (53)	60 (53.6)	
ALP (IU/L) (%)			
Normal	119 (95.2)	145 (98.6)	0.094
Hyper	6 (4.8)	2 (1.4)	

PD=Parkinson's disease; 25OHD=25-hydroxyvitamin D; PTH=Parathyroid hormone; ALP=Alkaline phosphates

Table 2: Predictive parameters in Parkinson disease

Variables	Odd ratio (CI, lower-upper)	P value
Sex		
Male	2.53 (1.276-5.037)	0.008
Female	1	
Age		
Control	1.021 (0.994-1.048)	0.132
PD	1	
25OHD		
Normal	1.577 (0.797-3.119)	0.191
Hypo	1	
PTH		
Normal	1	0.265
Hyper	0.9 (0.281-1.400)	
ALP		
Normal	451 (0.075-2.718)	0.385
Hyper	1	

PD=Parkinson's disease; 25OHD=25-hydroxyvitamin D; PTH=Parathyroid hormone; ALP=Alkaline phosphates; CI=Confidence interval

than age- and sex matched control was observed but the only factor that plays a role in the risk of disease is gender so, men are more likely to develop the disease and this is completely accordance with previous research.^[18]

Calcium disturbance eventually causes a decrease in calcium concentration in extracellular fluid compartments, ensuing in organ-specific modulation of calcium-sensing receptor activity,^[19] however, our result did not support this hypothesis that the low-level of calcium could increase intracellular calcium and neural cell death in PD.^[17,20] Meanwhile, contrary results have presented that removal of extracellular calcium reduces the neural degeneration in cortical cell cultures.^[21] Furthermore, it has been reported that PTH levels are enhanced in patients with 25OHD deficiency and there is a negative association between PTH and 25OHD levels.^[22] Low 25OHD levels accompanied by compensatory hyperparathyroidism,^[23] but in our study due to lack of 25OHD and calcium deficiency in PD patients than control, we could explain why the level of PTH has not changed appreciably.

Serum 25OHD is resulting from both dietary intake and sunlight-induced production by the skin,^[24] and as the most plentiful circulating vitamin D metabolite,^[25] it represents the most sensitive and useful index of the body's vitamin D supply. Although, some lines of *in-vitro* evidence suggest a link between vitamin deficiency and pathogenesis of PD^[1] but *in-vivo* association between vitamin D status and PD is still a contentious issue. In this study, serum vitamin D level in healthy individuals and PD patients did not differ significantly. Most of the previous studies, chose their sample from hospitalized patients^[10,26] that indicate they have lower mean vitamin D levels than age-matched participants recruited from the community but participants

in this study were enlisted from the out-patient and clinical wards of a hospital in Isfahan city and this difference may be related to this different situation.

The mean baseline 25OHD concentration in PD patients for our case-control study (28.1 ± 1.45 ng/mL) was also slightly higher than one cross-sectional study that reported by Sato *et al.* (22 ng/mL ± 1.01),^[11] and another cohort study (26.3 ng/mL) in subjects with early PD (Hoehn and Yahr stages 1 and 2).^[17] One reason for this difference is related to age, ethnicity, and sex variation between studies. The mean age in our study was about 10 years younger than the mean age previously reports by Sato *et al.*,^[11] confirming that increasing age is a reasonable claim for low vitamin D levels in old individuals. Moreover, women in the United States^[27] and Iran^[28] tend to have slightly lower vitamin D concentrations than men, which is another possible explanation for the observed difference between our and Evatt's study (M = 70% and F = 29.4% and M = 64.3% and F = 35.7%, respectively).

This study has a number of potential weaknesses; the limited information on dietary intake of vitamin D and calcium is of potential concern. Further extensive longitudinal studies are needed to establish a cause-effect association between PD and mineral elements such as Ca, vitamin D, and phosphorus.

CONCLUSION

Our study couldn't support some previous studies, which concluded the possibility role of some elements related to bone metabolism such as vitamin D in PD, regarding our study was designed for younger patients and mostly in early disease to decrease the immobility and other disorders effects related to chronic situations of PD. Hence, we concluded that previous reports, indicating significantly different between PD cases and control group for biochemical levels related to bone metabolism, are probably due to effects of PD and not as a direct role for PD pathogenesis.

REFERENCES

1. Newmark HL, Newmark J. Vitamin D and Parkinson's disease: A hypothesis. *Mov Disord* 2007;22:461-8.
2. Jenner P. Oxidative stress in parkinson's disease. *Ann Neurol* 2003;53:S26-36.
3. Wuillner U, Klockgether T. Inflammation in Parkinson's disease. *J Neurol* 2003;250:135-8.
4. Schapira AH. Mitochondrial dysfunction in Parkinson's disease. *Cell Death Differ* 2007;14:1261-6.
5. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol* 2006;5:525-35.
6. Mouatt-Prigent A, Agid Y, Hirsch EC. Does the calcium binding protein calretinin protect dopaminergic neurons against degeneration in Parkinson's disease? *Brain Res* 1994;668:62-70.
7. Surmeier DJ, Guzman JN, Sanchez-Padilla J, Schumacker PT.

- The role of calcium and mitochondrial oxidant stress in the loss of substantia nigra pars compacta dopaminergic neurons in Parkinson's disease. *Neuroscience* 2011;198:221-31.
8. Abou-Raya S, Helmii M, Abou-Raya A. Bone and mineral metabolism in older adults with Parkinson's disease. *Age Ageing* 2009;38:675-80.
 9. Clouston WM, Lloyd HM. Immobilization-induced hypercalcemia and regional osteoporosis. *Clin Orthop Relat Res* 1987;216:247-52.
 10. Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Abnormal bone and calcium metabolism in immobilized Parkinson's disease patients. *Mov Disord* 2005;20:1598-603.
 11. Sato Y, Kikuyama M, Oizumi K. High prevalence of vitamin D deficiency and reduced bone mass in Parkinson's disease. *Neurology* 1997;49:1273-8.
 12. Evatt ML, DeLong MR, Khazai N, Rosen A, Triche S, Tangpricha V. Prevalence of vitamin D insufficiency in patients with Parkinson disease and Alzheimer disease. *Arch Neurol* 2008;65:1348-52.
 13. Sato Y, Kaji M, Tsuru T, Satoh K, Kondo I. Vitamin K deficiency and osteopenia in vitamin D-deficient elderly women with Parkinson's disease. *Arch Phys Med Rehabil* 2002;83:86-91.
 14. Suzuki M, Yoshioka M, Hashimoto M, Murakami M, Kawasaki K, Noya M, *et al.* 25-hydroxyvitamin D, vitamin D receptor gene polymorphisms, and severity of Parkinson's disease. *Mov Disord* 2012;27:264-71.
 15. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol* 1999;56:33-9.
 16. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266-81.
 17. Evatt ML, DeLong MR, Kumari M, Auinger P, McDermott MP, Tangpricha V, *et al.* High prevalence of hypovitaminosis D status in patients with early Parkinson disease. *Arch Neurol* 2011;68:314-9.
 18. Taylor KS, Cook JA, Counsell CE. Heterogeneity in male to female risk for Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2007;78:905-6.
 19. Peterlik M, Cross HS. Vitamin D and calcium deficits predispose for multiple chronic diseases. *Eur J Clin Invest* 2005;35:290-304.
 20. Barbagallo M, Dominguez LJ, Licata G, Resnick LM. Effects of aging on serum ionized and cytosolic free calcium: Relation to hypertension and diabetes. *Hypertension* 1999;34:902-6.
 21. Mehta A, Prabhakar M, Kumar P, Deshmukh R, Sharma PL. Excitotoxicity: Bridge to various triggers in neurodegenerative disorders. *Eur J Pharmacol* 2013;698:6-18.
 22. Sato Y, Kaji M, Tsuru T, Oizumi K. Risk factors for hip fracture among elderly patients with Parkinson's disease. *J Neurol Sci* 2001;182:89-93.
 23. Himmelstein S, Clemens TL, Rubin A, Lindsay R. Vitamin D supplementation in elderly nursing home residents increases 25(OH)D but not 1,25(OH)₂D. *Am J Clin Nutr* 1990;52:701-6.
 24. Beadle PC. Sunlight, ozone and vitamin D. *Br J Dermatol* 1977;97:585-91.
 25. Nieves J, Cosman F, Herbert J, Shen V, Lindsay R. High prevalence of vitamin D deficiency and reduced bone mass in multiple sclerosis. *Neurology* 1994;44:1687-92.
 26. Sato Y, Asoh T, Oizumi K. High prevalence of vitamin D deficiency and reduced bone mass in elderly women with Alzheimer's disease. *Bone* 1998;23:555-7.
 27. Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. *Arch Intern Med* 2009;169:626-32.
 28. Hovsepian S, Amini M, Aminorroaya A, Amini P, Iraj B. Prevalence of vitamin D deficiency among adult population of Isfahan City, Iran. *J Health Popul Nutr* 2011;29:149-55.

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