

Vitamin D reduces falls and hip fractures in vascular Parkinsonism but not in Parkinson's disease

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Purpose: Vitamin D supplementation is suggested to reduce the risk of falls in older institutionalized or ambulatory individuals by 20%. The present study was undertaken to address the reduced risk, by vitamin D supplementation, of falls and hip fractures in patients with vascular Parkinsonism (VP) and Parkinson's disease (PD).

Patients and methods: In the open-label-study, 94 elderly patients with VP and 92 age-matched patients with PD were followed for 2 years. All patients received 1200 IU ergocalciferol daily. The number of falls per person and incidence of hip fractures were compared between the two groups.

Results: At baseline, serum 25-hydroxyvitamin D (25-OHD) levels were in the deficient range (<25 nmol/L) in all patients, and vitamin D treatment enhanced serum 25-OHD and 1,25-dihydroxyvitamin D levels in both groups. Improved muscle strength of lower extremities was observed in both groups. There was significant difference between the two groups in the number of falls per subject during the 2 years (1.9 ± 0.5 in the PD group and 0.8 ± 0.4 in the VP group, $P < 0.001$). Hip fractures occurred in seven of 88 in the PD group and one in 90 of the VP group during the 2-year study period ($P = 0.035$).

Conclusion: It is suggested that vitamin D decreases falls and hip fractures in VP by increasing muscle strength but not in PD.

Keywords: fall, hip fracture, Parkinson's disease, vascular Parkinsonism, vitamin D

Introduction

Recent advances in diagnosis and treatment have prolonged survival in elderly patients with Parkinson's disease (PD), and patients' physical states have become increasingly important in PD management. Previous studies¹⁻⁵ demonstrated a high incidence of falls and hip fractures in PD patients, particularly in elderly women.³ Prolonged survival may contribute to the decreased bone mineral density (BMD) and increased risk of fractures seen in the PD population. Several reports have documented low BMD of the lumbar vertebrae,⁵ hip joint,⁶ or second metacarpal^{7,8} in PD patients, with severe osteoporosis being more prevalent at higher Hoehn and Yahr stages.^{5,7}

We previously demonstrated that 25-hydroxyvitamin D (25-OHD) deficiency (less than 25 nmol/L) due to sunlight deprivation induces compensatory hyperparathyroidism, which further contributes to reduced BMD in PD patients, particularly those who are functionally dependent.⁷ However, when serum 25-OHD was in an insufficient range (25–47 nmol/L), immobilization-induced hypercalcemia inhibited parathyroid hormone (PTH) secretion.⁷ Compensatory hyperparathyroidism associated with deficient 25-OHD levels and immobilization induce increased bone resorption and contribute

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to reduced BMD and occurrence of hip fractures.^{8,9} On the other hand, patients with vascular Parkinsonism (VP) are similar in terms of abnormal bone and calcium metabolism and have a high risk of falls and hip fractures (Sato et al, unpublished data, 2003). Gait and balance disorders causing falls are common in PD and VP, but fall pathophysiology is still poorly understood.

Prevention of a hip fracture, which is likely to offset gains from rehabilitation and preclude new gains, is extremely important in PD and VP. It is suggested that vitamin D supplementation reduces the risk of falls in older institutionalized or ambulatory individuals.¹⁰ Previously, the moderate protective effect of vitamin D on a fracture risk was attributed primarily to BMD changes.¹¹ Vitamin D may increase muscle strength by improving atrophy of type II muscle fibers, which may lead to decreased falls and hip fractures.¹²

We previously found that PD patients had remarkably low serum 25-OHD levels,⁸ and many of them had a concentration of less than 25 nmol/L. Many such patients also had very low serum levels of 1,25-dihydroxyvitamin D (1,25-[OH]2D), and immobilization-induced hypercalcemia may be responsible for inhibition of renal synthesis of 1,25-[OH]2D.⁸

In the present study, we focused on vitamin D treatment in PD and VP for the effective prevention of falls and hip fracture. We conducted a 2-year case control study to evaluate the efficacy of ergocalciferol therapy in reducing the risk of falls in elderly patients with PD and VP.

Materials and methods

Study population

The study was approved by the local ethics committee of Mitate Hospital, Tagawa, Japan, and informed consent was obtained from all subjects in the presence of a witness.

This study compared the occurrence of falls in the two groups (PD and VP) administered ergocalciferol. Consecutive studies included 92 elderly patients with PD and 94 elderly patients with VP followed in the neurology clinic of Mitate Hospital, which provides comprehensive long-term outpatient care for neurology. Patients matched for sex and age with diagnoses of PD and VP were included in the study. No PD patients underwent deep brain stimulation surgery as there is no equipment for this surgery in Mitate or surrounding hospitals.

The diagnostic criteria of VP were as follows: (1) Parkinsonism, defined as bradykinesia, and at least one of the following: rest tremor, rigidity, or postural instability; (2) cerebrovascular disease, defined as evidence of relevant cerebrovascular disease by brain imaging or the presence

of focal signs or symptoms that are consistent with stroke; (3) a relationship between (1 and 2): an acute or delayed progressive onset of Parkinsonism (within 1 year) after stroke with evidence of infarcts that increase the basal ganglion motor output or decrease the thalamocortical drive directly, or an insidious onset of Parkinsonism with extensive subcortical white matter lesions, bilateral symptoms at the onset, and the presence of early shuffling gait or early cognitive dysfunction.¹³

Patients of both groups were selected by detailed examination of case notes of patients to match patients with respect to age, sex, and the motor part of the Unified Parkinson's Disease Rating Scale III (UPDRS III).¹⁴ Exclusion criteria included inability to walk and previous history of hip fracture. Other exclusion criteria included peripheral neuropathy, renal insufficiency (serum creatinine concentration ≥ 1.5 mg/dL), hepatic insufficiency, or cardiac failure. Patients were excluded if they had received any drugs known to alter vitamin D metabolism, such as anticonvulsants, calcium, or vitamins D and K, during the 12 months preceding the study. No attempt was made to alter subjects' diet or activity during the study.

At baseline, we determined body mass index (BMI), and UPDRS III.¹⁴ Sunlight exposure during the preceding year was assessed and graded as less than 15 minutes per week or longer.¹⁵ A physical therapist who was blinded to information concerning the patients evaluated the muscle strength of the lateral and medial rotators of the hip, and flexion and extension of thigh with hip and knee flexed 90° using the British Medical Research Council (MRC) scale.¹⁶ The British MRC scale defines a score of 0 as no contraction of the tested muscle while a score of 5 represents normal power. The total points for muscle strength of the four different movements of the hip joint were calculated for each patient. The muscle strength was evaluated at baseline, and 1 and 2 years later.

Patients who fell at least once in the 3 months before recruitment were defined as "fallers." Falls were defined as incidents in which a subject fell due to an unexpected loss of balance. The number of falls per subject was also recorded during the 2-year follow-up period. Falls were registered by means of monthly "fall calendars." The participants were instructed to complete the calendar daily, marking an "X" for each fall on the date that the fall occurred. If the patient suffered dementia, the calendar was completed by family members.

All patients received a daily dose of 1200 IU ergocalciferol. We used ergocalciferol as a part of the synthesized vitamin powder commercially available in Japan.

Ergocalciferol was administered twice per day with breakfast and dinner. Doses of ergocalciferol were not adjusted for each patient and no dose adjustments were made at any time during the study. Patients were not allowed to take any other drugs that could affect bone and calcium metabolism. Adherence to study medication was assessed by pill count of returned tablets. Follow-up assessment of the patients was performed by two physicians who did not participate in the initial randomization. Both groups were observed for 2 years. General medical evaluation and serum indices of bone metabolism were assessed upon study entry and after 2 years. Four patients in the PD group and four in the VP group dropped out or withdrew from the study due to noncompliance, loss to follow-up, intercurrent illness, or death. Thus, a total of 178 patients (88 in the PD group and 90 in the VP group) completed the trial.

A blood sample was obtained from each patient after an overnight fast. Blood samples were analyzed for ionized calcium, intact PTH, and 25-OHD and 1,25-[OH]₂D as described previously.¹⁷ The biochemical data, at the start and 1 and 2 years later, of the patients who completed the cohort were analyzed.

Statistical analysis

All statistical analyses were performed using the StatView J 5.0 software package (Abacus Concepts, Berkeley, CA, USA). Values are given as the mean \pm SD unless otherwise indicated. Group differences of the categorical data were tested by χ^2 analyses or Fisher's exact method. The unpaired *t*-test was used to determine the differences between the two groups. Spearman's rank correlation coefficients were calculated to

determine the relationships between UPDRS III or strength scale of hip muscle and 25-OHD levels. The two groups were compared with respect to their laboratory values by using Wilcoxon rank-sum test. The difference in the incidence of hip fractures between the two groups during the 2 years was tested by Fisher's exact test. *P*-values of less than 5% were considered statistically significant.

Results

Demographic and baseline clinical characteristics of study subjects

Characteristics of the study population are given in Tables 1 and 2. Patient characteristics, number of falls, MRC hip strength, sunlight exposure, and laboratory values did not differ between the two groups at baseline. Mean serum 25-OHD concentrations were 22 nmol/L. Serum ionized calcium levels were high, while PTH and 1,25-[OH]₂D concentrations were low as compared to the reference range of normal Japanese population.⁸ When the two patient groups were analyzed together, ionized calcium concentrations correlated negatively with UPDRS III ($r = -0.412$, $P < 0.0001$) and PTH ($r = -0.574$, $P < 0.0001$). There was no correlation between serum 25-OHD and PTH ($r = 0.070$, $P = 0.49$).

When the PD and VP groups were analyzed together, 25-OHD concentrations correlated positively with UPDRS III ($r = 0.255$, $P = 0.0122$) and strength scale of hip muscle ($r = 0.568$, $P < 0.0001$).

Fallers and hip fracture incidence

Table 2 summarizes time-dependent changes in the frequency of fallers who fell at least once in 3 months. The numbers

Table 1 Demographic and baseline clinical characteristics of the patients with Parkinson's disease and vascular Parkinsonism at study entry

Characteristic	Parkinson's disease (n = 92)	Vascular Parkinsonism (n = 94)	P-value*
Age (years)	73.6 \pm 5.9	73.9 \pm 6.2	0.80
Men (n = 105), n (%)	49 (53)	56 (60)	0.65 [†]
Duration of illness (years)	4.8 \pm 2.9	5.0 \pm 3.1	0.68
Hoehn and Yahr stage ¹⁸	3.2 \pm 1.2	3.3 \pm 1.6	0.75
UPDRS III (motor function score) ¹⁴	53.4 \pm 12.8	55.8 \pm 15.1	0.71
Faller, n (%) [‡]	33 (36)	32 (34)	0.86 [†]
Strength scale of hip muscle [§]	3.8 \pm 1.4	3.9 \pm 1.6	0.64
Sunlight exposure/week, n (%)			
> 15 minutes	4 (4)	3 (3)	
< 15 minutes	12 (13)	15 (16)	
None	76 (83)	76 (81)	0.80 [†]

Notes: Values are mean \pm standard deviation. *Unpaired *t*-test; [†]Fisher's exact test; [‡]patients who fell at least once in the 3 months before recruitment or study period were defined as "fallers;" [§]the British Medical Research Council scale defines a score of 0 as no contraction of the four tested muscles while a score of 5 represents normal power of the hip muscle.¹⁶ The values are the average point of four muscles.

Abbreviation: UPDRS III, Unified Parkinson's Disease Rating Scale III.

Table 2 Falls and biochemical tests in Parkinson's disease and vascular Parkinsonism groups at baseline and after 1 and 2 years of follow-up

Biochemical indices and group	Follow-up		
	Baseline	1 year	2 years
Faller, n (%)			
Parkinson's disease	33 (36)	30 (33)*	31 (35)*‡
Vascular Parkinsonism	32 (34)	13 (14) [†]	14 (16) [†]
Strength scale of hip muscle[†]			
Parkinson's disease	3.8 ± 1.4	4.4 ± 1.2 [†]	4.5 ± 1.6 [†]
Vascular Parkinsonism	3.9 ± 1.6	4.5 ± 1.5 [†]	4.4 ± 1.3 [†]
Ionized calcium (mmol/L)			
Parkinson's disease	1.32 ± 0.06	1.33 ± 0.07 [§]	1.33 ± 0.08 [§]
Vascular Parkinsonism	1.31 ± 0.08	1.31 ± 0.09	1.32 ± 0.10
Intact parathyroid hormone (ng/L)			
Parkinson's disease	32.1 ± 12.1	33.0 ± 9.9 [§]	36.3 ± 4.5 [§]
Vascular Parkinsonism	30.5 ± 11.5	35.6 ± 6.0	34.2 ± 3.9
25-hydroxyvitamin D (nmol/L)			
Parkinson's disease	23.0 ± 10.7	56.2 ± 6.2 [†]	58.9 ± 7.0 ^{†§}
Vascular Parkinsonism	22.7 ± 9.7	54.9 ± 8.2 [†]	59.7 ± 8.7 [†]
1,25-dihydroxyvitamin D (pmol/L)			
Parkinson's disease	81.1 ± 28.1	98.8 ± 26.8 [†]	102.7 ± 22.6 ^{†§}
Vascular Parkinsonism	87.1 ± 29.1	104.8 ± 25.7	108.2 ± 21.1 [†]

Notes: Values are mean ± SD. * $P < 0.001$ versus vascular Parkinsonism; [†] $P < 0.001$ for the comparison with the baseline value; [‡]not significant for the comparison with the baseline value; [§]not significant versus vascular Parkinsonism; ^{||}patients who fell at least once in the 3 months before recruitment or study period were defined as "fallers;" [†]the British Medical Research Council scale defines a score of 0 as no contraction of the four tested muscles while a score of 5 represents normal power of the hip muscle.¹⁶ The reference ranges of a healthy elderly person:^{19,20} ionized calcium, 1.22–1.27 mmol/L; intact parathyroid hormone, 35–52 ng/L; 25-hydroxyvitamin D, 47.2–62.2 nmol/L; 1,25-dihydroxyvitamin D, 102.4–147.7 pmol/L.

after 12 and 24 months remained unchanged in PD patients and decreased in VP patients ($P < 0.001$). There was a significant difference between the two groups in the number of falls per subject during the 2 years (1.9 ± 0.5 in the PD group and 0.8 ± 0.4 in the VP group, $P < 0.001$).

Hip fractures caused by falls occurred in seven cases in the PD group, and in one case in the VP group, during the 2-year study period ($P = 0.035$). The number of hip fractures per 1000 patient-years was 21 and 152 for the VP and PD groups, respectively.

Muscle strength and serum indices of bone metabolism

During the 2-year period, significant increase of muscle strength was observed in both groups. During the 2-year period, serum 25-OHD levels had increased to the normal range in both groups. In both groups, serum PTH concentration increased but remained low as compared to the reference range, while serum ionized calcium concentration decreased but remained high as compared to the reference range. Serum 25-[OH]2D levels had increased in both groups (Table 2).

Discussion

Prevention of fractures is one of the important issues in the management of PD and VP patients. There are multiple factors for falls in PD, including postural instability as well as psychological and physical complications.^{21,22} The high incidence of hip fractures in elderly PD and VP patients may be attributed to frequent falls and osteoporosis due to hypovitaminosis D and disuse.^{1,2,7} The present study demonstrated that vitamin D reduced the number of falls in VP but did not affect falls in PD during the 2 years. As a result, hip fracture incidence may be low in VP and high in PD. Fall incidence in PD did not increase during the 2 years (data not shown), despite PD being a progressive disease. The study suggests that falls in PD are not caused by hypovitaminosis D but caused by PD specific extrapyramidal system (EPS) abnormalities.

This is the first study that documents a reduction in falls among frail VP patients but not in PD patients with a single medication over 2 years. Previous studies on the relationship between vitamin D and muscle strength in elderly subjects demonstrated the beneficial effect in relation to muscle strength and balance. One such study demonstrated the effectiveness of vitamin D in restoring musculoskeletal function in institutionalized elderly women.²³ Also, 2-month treatment with vitamin D and calcium was found to decrease both body sway and falls in ambulatory elderly women.²⁴ It has been demonstrated that serum 25-OHD levels are low in elderly fallers²⁵ and muscle strength is higher in the ambulatory elderly with higher 25-[OH]2D levels.²⁶ In the present study, by administering vitamin D, we found improvement in muscle strength in VP and PD patients who had deficient levels of serum 25-OHD before the therapy. Severe vitamin D deficiency is common in PD and VP⁹ and type II fiber atrophy is one of the characteristics of vitamin D deficient myopathy.²⁷ We observed improvement in muscle strength in VP and PD patients to whom vitamin D had been administered.

The effect of vitamin D on muscle strength may be explained by its direct effects on muscle tissues.²⁸ These effects may be mediated by de novo protein synthesis, affecting muscle cell growth.²⁹ Because this effect on muscle tissues seems to result in clinical improvement even after a short-term intervention,^{12,30} it is of major clinical interest if vitamin D may be effective for the prevention of falls and thus fractures in elderly people. Indeed, a study showed that in vitamin D-deficient subjects, severely impaired muscle function may be present even before biochemical signs of bone disease develops.³¹

Despite the similar effectiveness of vitamin D on muscle strength in both PD and VP, the reason for the

different incidence of falls between the two groups is unclear. We postulate that falls in PD are not caused by hypovitaminosis D-induced muscular weakness, but are caused by PD-specific EPS abnormalities, while vitamin D deficiency causing muscular weakness rather than EPS disorder causes falls in VP.

Kalra et al reviewed 25 articles about differentiating VP from idiopathic PD and concluded there were no accepted international diagnostic criteria for VP.³² Although the applied diagnostic criteria for VP in the present study is not a universally accepted international standard, we believe that the criteria is better than the other 24 articles describing criteria of VP.

Hip fracture is a serious complication in VP, leading to surgical treatment that may be complicated by pulmonary embolism, fat embolism syndrome, pneumonia, urinary tract infections, and deep vein thrombosis. Also, a bedridden state after surgery is not uncommon.³³ Thus, ergocalciferol administration for VP is of benefit in the prevention of hip fracture and the necessity for surgical treatment leading to potential complications and a bedridden state. On the other hand, open-label-study and absent data of BMD and muscle biopsy and/or electrophysiology before and after the treatment are the limitations of the study. However, our previous study¹² in patients following stroke with hypovitaminosis D showed increases in the relative number and size of type II muscle fibers and improved muscle strength in the vitamin D-treated (1000 IU ergocalciferol daily) group over 2 years. Therefore, we believe vitamin D may increase muscle strength by improving atrophy of type II muscle fibers, which may lead to decreased falls and hip fractures. In future studies, randomized controlled trials measuring BMD and performing muscle biopsy and/or electrophysiology should be considered. Also, we did not study age-matched controls for proper comparison and to demonstrate the effect of vitamin D treatment. This is another study limitation not indicating how much the risk of falling was reduced in the cohorts study. We did not assess autonomic neuropathy or visual problems in the present study, which is an additional study limitation.

Conclusion

Vitamin D supplementation in VP patients with low serum vitamin D causes decreased risk for falls, while such a phenomenon is not observed in PD patients. Treatment with ergocalciferol may be safe and effective in restoring muscular strength, which may reduce falls and the risk of fractures in VP.

Disclosure

The authors report no conflicts of interest in this work.

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