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EDITORIAL

Strategy for prevention of hip fractures in patients with Parkinson's disease

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Abstract

Hypovitaminosis D and K due to malnutrition or sunlight deprivation, increased bone resorption due to immobilization, low bone mineral density (BMD) and an increased risk of falls may contribute to an increased risk of hip fractures in patients with Parkinson's disease. The purpose of the present study was to clarify the efficacy of interventions intended to prevent hip fractures in elderly patients with Parkinson's disease. PubMed was used to search the literature for randomized controlled trials (RCTs) regarding Parkinson's disease and hip fractures. The inclusion criteria were 50 or more subjects per group and a study period of 1 year or longer. Five RCTs were identified and the relative risk and 95% confidence interval were calculated for individual RCTs. Sunlight exposure increased serum hydroxyvitamin D [25(OH)D] concentration, improved motor function, decreased bone resorption and increased BMD. Alendronate or risedronate with vitamin D supplementation increased serum 25(OH)D concentration, strongly decreased bone resorption and increased BMD. Menatetrenone (vitamin K_2) decreased serum undercarboxylated osteocalcin concentration, decreased bone resorption and increased BMD. Sunlight exposure (men and women), menatetrenone (women), alendronate and risedronate with vitamin D supplementation (women) significantly reduced the incidence of hip fractures. The respective RRs (95% confidence intervals) according to the intention-to-treat analysis were 0.27 (0.08, 0.96), 0.13 (0.02, 0.97), 0.29 (0.10, 0.85) and 0.20 (0.06, 0.68). Interventions, including sunlight exposure, menatetrenone and oral bisphosphonates with vitamin D supplementation, have a protective effect against hip fractures elderly patients with Parkinson's disease.

Key words: Vitamin D; Vitamin K; Hip fractures; Parkinson's disease; Mortality

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INTRODUCTION

Parkinson's disease is a movement disorder characterized by tremor, rigidity, akinesia and loss of postural reflexes, leading to immobility and frequent falls[1,2]. Evidence has indicated a high incidence of hip fractures in patients with Parkinson's disease, with falls being a major cause[3-5]. This is especially true in elderly women and the odds ratio of hip fractures in elderly women is reported to be 9.4[5,6]. Hip fractures are associated with higher medical

costs[7]. Functional recovery after hip fractures in patients with osteoporosis is poor[8-10] and elderly patients have increased mortality after hip fractures[11]. Thus, strategies protecting against hip fractures should be established in elderly patients with Parkinson's disease.

Hypovitaminosis D and K due to malnutrition or sunlight deprivation, increased bone resorption due to immobilization, low bone mineral density (BMD) and an increased risk of falls may increase the risk of hip fractures in elderly patients with Parkinson's disease[12-16]. Hypovitaminosis D is known to increase the risk of falls in the elderly[17-19]. An immobilization-induced increase in bone resorption causes hypercalcemia, which may inhibit the compensatory hyperparathyroidism that otherwise could occur in response to hypovitaminosis D. Sunlight exposure, vitamin D and K supplementation, and potent anti-resorptive drugs are considered to be effective strategies to prevent hip fractures. Recent evidence has shown the efficacy of interventions protective against hip fractures in elderly patients with Parkinson's disease[12-16]. The purpose of the present study was to clarify the efficacy of these interventions in elderly patients with Parkinson's disease by reviewing the literature to date.

LITERATURE SEARCH

PubMed was used to search the literature for randomized controlled trials (RCTs) of interventions affecting the incidence of hip fractures in patients with Parkinson's disease. The following terms were used: Parkinson's disease and fracture. The inclusion criteria were 50 or more subjects per group and a study period of 1 year or longer. Non-English papers were excluded.

RCTs showing efficacy of interventions against hip fractures were identified and the efficacy of interventions against hip fractures was analyzed using the data from the RCTs. The relative risk (RR) and 95% confidence interval (CI) were calculated for individual trials. The statistical analyses were performed using PC SAS v8.2.

IDENTIFIED RANDOMIZED CONTROLLED TRIALS

Five RCTs were found dealing with Parkinson's disease and hip fractures[12-16]. Table 1 shows the details of the identified RCTs: one RCT for sunlight exposure, one RCT for menatetrenone (vitamin K_2), one RCT for alendronate and two RCTs for risedronate. All of the RCTs were performed in Japan. The mean ages of the subjects were 71.3-75.4 years, reflecting studies in the elderly population. The mean durations of their illness (Parkinson's disease) were 4.1-5.1 years. The studies lasted for 1-2 years. Patients were exposed to sunlight on 452 clear weather days (3231 min/year) during the 2 year study period. The doses of menatetrenone (45 mg/d), alendronate (5 mg/d) and risedronate (2.5 mg/d or 17.5 mg/wk) used in the RCTs were approved by the Health, Labor and Welfare Ministry of Japan. Calcium supplementation was not provided in any RCT because such a therapy could aggravate immobilization-induced hypercalcemia and decrease renal synthesis of 1,25 dihydroxyvitamin D [1,25$(OH)_2$D]. Vitamin D (ergocalciferol 1000 IU/d) supplementation was provided in three RCTs for alendronate and risedronate (potent anti-resorptive drugs). During the trials, 4.3%-9.7% of patients were dropped because of death or intercurrent illness, noncompliance or loss to follow-up. No severe adverse events were observed.

EFFICACY OF SUNLIGHT EXPOSURE AGAINST HIP FRACTURES

Study subjects were men and women. Serum 25(OH)D concentration, muscle strength, motor function and metacarpal BMD increased in the sunlight exposure group and decreased in the usual lifestyle group[12]. Urinary deoxypyridinoline concentration decreased in the sunlight exposure group and increased in the usual lifestyle group. Respective changes in serum 25(OH)D concentration were +92.6% and -51.9%. Respective percentage changes in metacarpal BMD were +3.8% and -2.6%. The RR (95% CI) for hip fractures in the sunlight exposure group compared with the usual lifestyle group was 0.27 (0.08, 0.95) for the intent-to-treat (ITT) set and 0.27 (0.08, 0.95) for the per protocol set (PPS) (Table 2), suggesting a significant reduction in the risk of hip fractures after sunlight exposure therapy.

EFFICACY OF MENATETRENONE AGAINST HIP FRACTURES

Study subjects were women. Serum vitamin K_2 concentration increased and serum undercarboxylated osteocalcin (ucOC) decreased in the menatetrenone group compared with the non-treatment group[13]. Respective changes in serum vitamin K_2 concentration were +259.8% and -1.8%. Respective changes in serum ucOC concentration were -46.7% and +3.3%. Urinary deoxypyridinoline and serum ionized calcium concentrations decreased, intact PTH concentrations increased and metacarpal BMD increased in the menatetrenone group compared with the non-treatment group. Respective percentage changes in metacarpal BMD were +0.9% and -4.3%. The RR (95% CI) of hip fractures after menatetrenone treatment compared with non-treatment was 0.13 (0.02, 0.97) for the ITT set and 0.12 (0.02, 0.93) for the PPS (Table 2), suggesting a significant reduction in the risk for hip fractures after menatetrenone therapy.

EFFICACY OF ALENDRONATE AGAINST HIP FRACTURES

Study subjects were women. Serum 25(OH)D concentra-

Table 1 Identified randomized controlled trials of efficacy of interventions against hip fractures in patients with Parkinson's disease

Interventions	Groups	Number of study subjects			Average age (yr)	Average duration of illness (yr)	Vitamin D supplementation	Study period (yr)
		Randomized	Dropped out	Completed				
Sunlight exposure[12]	Sunlight exposure	162	6	156	75.4	4.2	None	2
(men/women)	Usual lifestyle	162	8	154	75.2	4.1		
menatetrenone[13]	Menatetrenone	60	4	56	72.3	4.8	None	1
(women)	Non-treatment	60	6	54	71.6	4.9		
Daily alendronate[14]	Alendronate	144	13	131	72.2	5.1	Ergocalciferol (1000 IU/d)	2
(women)	Placebo	144	15	129	72.2	5.1		
Daily risedronate[15]	Risedronate	121	10	111	71.3	4.9	Ergocalciferol (1000 IU/d)	2
(men)	Placebo	121	9	112	71.3	4.9		
Weekly risedronate[16]	Risedronate	136	10	126	74.4	4.8	Ergocalciferol (1000 IU/d)	2
(women)	Placebo	136	12	124	74.4	4.9		

Table 2 Efficacy of interventions against hip fractures in patients with Parkinson's disease

Interventions	Relative risk (95% confidence interval)	
	ITT set	PPS
Sunlight exposure[12]	0.27 (0.08, 0.96)	0.27 (0.08, 0.95)
Menatetrenone[13]	0.13 (0.02, 0.97)	0.12 (0.02, 0.93)
Alendronate (Daily)[14]	0.29 (0.10, 0.85)	0.28 (0.10, 0.83)
Risedronate (Daily)[15]	0.33 (0.09, 1.20)	0.34 (0.09, 1.21)
Risedronate (Weekly)[16]	0.20 (0.06, 0.68)	0.20 (0.06, 0.66)

ITT: Intention-to-treat, PPS: Per-protocol set.

tion increased, urinary deoxypyridinoline and serum ionized calcium concentrations decreased, and metacarpal BMD increased in the alendronate + vitamin D supplementation group[14]. Serum 25(OH)D, urinary deoxypyridinoline and serum ionized calcium concentrations increased, and metacarpal BMD decreased in the placebo + vitamin D supplementation group. Respective changes in serum 25(OH)D concentration were +209.8% and +209.5%. Respective changes in urinary deoxypyridinoline concentration were -38.1% and +14.0%. Respective percentage changes in metacarpal BMD were +3.1% and -2.8%. The RR (95% CI) of hip fractures after alendronate compared with placebo was 0.29 (0.10, 0.85) for the ITT set and 0.28 (0.10, 0.83) for the PPS (Table 2), suggesting a significant reduction in the risk of hip fractures after alendronate therapy with vitamin D supplementation.

EFFICACY OF RISEDRONATE AGAINST HIP FRACTURES

Study subjects were men for the daily risedronate study and women for the weekly risedronate study[15,16]. Changes in serum 25(OH)D, urinary deoxypyridinoline, serum ionized calcium concentrations and metacarpal BMD in the two studies of daily and weekly risedronate + vitamin D supplementation (compared with placebo + vitamin D supplementation) were similar to those in the study of alendronate + vitamin D supplementation (compared with placebo + vitamin D supplementation) shown above. Respective changes in serum 25(OH)D concentration were +198.4% to +211.1% and +185.2% to +198.4%. Respective changes in urinary deoxypyridinoline concentration were -48.2% to -50.4% and +18.3% to +19.2%. Respective percentage changes in metacarpal BMD were +2.2% to +3.4% and -2.9% to -3.2%. The RR (95% CI) of hip fractures after daily risedronate compared with placebo in men was 0.33 (0.09, 1.20) for the ITT set and 0.34 (0.09, 1.21) for the PPS (Table 2). The RR (95% CI) of hip fractures after daily risedronate compared with placebo in women was 0.20 (0.06, 0.68) for the ITT set and 0.20 (0.06, 0.66) for the PPS (Table 2). These results suggested a significant reduction in the risk for hip fractures after risedronate therapy with vitamin D supplementation in elderly women with Parkinson's disease.

DISCUSSION

The present study clarified the efficacy of interventions (including sunlight exposure, menatetrenone and oral bisphosphonates with vitamin D supplementation) protecting against hip fractures in elderly patients with Parkinson's disease. Because hypovitaminosis D and K, increased bone resorption, low BMD and an increased risk of falls contribute to the risk for hip fractures in elderly patients with Parkinson's disease[12-16], these three interventions were suggested to be reasonable and effective for the management of bone health.

BMD, thickness, porosity and mean degree of mineralization in cortical bone may be important factors in determining the fracture risk at sites primarily composed of cortical bone such as the proximal femur in postmenopausal women with osteoporosis[20,21]. Because most hip fractures occur due to falls, motor function may also be an important factor in the risk of hip fractures. Serum 25(OH)D is derived from both dietary intake and sunlight-induced production by the skin[22,23]. The associations of hypovitaminosis D and vitamin D supplementation with the risk of falls have been confirmed in elderly persons[17-19]. Sunlight exposure improves hypovi-

taminosis D, leading to increases in muscle strength and motor function in men and women. A decrease in bone resorption induces an increase in cortical BMD. It is documented that cortical BMD correlates positively with serum 25(OH)D concentration, particularly in the subjects with vitamin D insufficiency[24]. Thus, improvements of muscle strength, motor function and cortical BMD might partly contribute to the prevention of hip fractures. Sunlight exposure appears to help prevent hip fractures in patients with Parkinson's disease and hypovitaminosis D due to malnutrition and sunlight deprivation.

Vitamin K deficiency, as indicated by a high serum ucOC concentration, and low BMD may independently contribute to the risk for hip fractures in elderly persons[25-27]. Menatetrenone improved hypovitaminosis K, decreased serum ucOC concentration, improved hypercalcemia and increased cortical BMD by decreasing bone resorption in women. Experimental studies showed the anti-resorptive effect of menatetrenone in various osteoporosis model animals[28,29]. A recent report showed that menatetrenone maintains bone strength of the femoral neck by improving femoral neck width and maintaining the indices of compression, bending and impact strength in healthy postmenopausal women[30]. Thus, improvements of cortical BMD, serum ucOC concentration and possibly bone geometry of the proximal femur might have partly contributed to the prevention of hip fractures. Menatetrenone appeared to be effective in preventing hip fractures in patients with Parkinson's disease and hypovitaminosis K. However, the magnitude of hip fracture risk reduction was quite high, probably because of the bias introduced by the use of a small sample size and the low intake of natto (fermented soy bean), in terms of severe vitamin K deficiency in the recruited subjects[31].

Alendronate or risedronate with vitamin D supplementation improved hypovitaminosis D, strongly decreased bone resorption, improved hypercalcemia and increased cortical BMD in men or women. Alendronate has been reported to strongly suppress bone resorption and improve femoral neck BMD, cortical thickness, cortical porosity and mean degree of mineralization of bone and thereby to prevent hip fractures in postmenopausal women with osteoporosis[20,21]. The greater the suppression of bone turnover and subsequent increase in BMD are, the better the drugs are at preventing nonvertebral fractures, including hip fractures[32]. Thus, improvements in the above parameters resulting from strong suppression of bone resorption[21] and a decrease in the risk of falls by vitamin D supplementation[17-19] may partly contribute to the prevention of hip fractures in women. Alendronate or risedronate and vitamin D supplementation appear to be quite effective for preventing hip fractures in women with Parkinson's disease and hypovitaminosis D, as well as increased bone resorption. However, risedronate and vitamin D supplementation did not significantly reduce the incidence of hip fractures in men, probably because of less than adequate statistical power due to the lower incidence of hip fractures in men (7.4% in the placebo + vitamin D supplementation group) compared with women (11.0% in the placebo + vitamin D supplementation group).

During the trials, 4.3-9.7% of patients were dropped because of death or intercurrent illness, noncompliance or loss to follow-up. However, no severe adverse events were observed, suggesting the safety of all interventions (sunlight exposure and pharmacotherapy such as menatetrenone and oral bisphosphonates) in elderly patients with Parkinson's disease.

Because patients with Parkinson's disease are prone to falls, not only sunlight exposure or vitamin D supplementation, but also hip protectors and exercise aiming at the prevention of falls may help reduce the incidence of hip fractures. However, exercise therapy may be difficult for patients with very advanced Parkinson's disease. Further studies are needed to confirm this suggestion.

CONCLUSION

The present study clarified the efficacy of three interventions, including sunlight exposure (men and women), menatetrenone (women) and oral bisphosphonates with vitamin D supplementation (women), protective against hip fractures in patients with Parkinson's disease. The risk of hip fractures was reduced 73% by sunlight exposure, 87% by menatetrenone treatment and 71-80% by oral bisphosphonate treatment. The efficacy of exercise and hip protectors remains to be established. These interventions might be difficult to perform but may help reduce the incidence of falls and possibility of hip fractures.

REFERENCES

1 **Aita JF**. Why patients with Parkinson's disease fall. *JAMA* 1982; **247**: 515-516
2 **Koller WC**, Glatt S, Vetere-Overfield B, Hassanein R. Falls and Parkinson's disease. *Clin Neuropharmacol* 1989; **12**: 98-105
3 **Chiu KY**, Pun WK, Luk KD, Chow SP. Sequential fractures of both hips in elderly patients--a prospective study. *J Trauma* 1992; **32**: 584-587
4 **Johnell O**, Melton LJ, Atkinson EJ, O'Fallon WM, Kurland LT. Fracture risk in patients with parkinsonism: a population-based study in Olmsted County, Minnesota. *Age Ageing* 1992; **21**: 32-38
5 **Grisso JA**, Kelsey JL, Strom BL, Chiu GY, Maislin G, O'Brien LA, Hoffman S, Kaplan F. Risk factors for falls as a cause of hip fracture in women. The Northeast Hip Fracture Study Group. *N Engl J Med* 1991; **324**: 1326-1331
6 **Eventov I**, Moreno M, Geller E, Tardiman R, Salama R. Hip fractures in patients with Parkinson's syndrome. *J Trauma* 1983; **23**: 98-101
7 **Nurmi I**, Narinen A, Lüthje P, Tanninen S. Cost analysis of hip fracture treatment among the elderly for the public health services: a 1-year prospective study in 106 consecutive patients. *Arch Orthop Trauma Surg* 2003; **123**: 551-554
8 **Holmes J**, House A. Psychiatric illness predicts poor outcome after surgery for hip fracture: a prospective cohort study. *Psychol Med* 2000; **30**: 921-929
9 **Matsueda M**, Ishii Y. The relationship between dementia score and ambulatory level after hip fracture in the elderly. *Am J Orthop* (*Belle Mead NJ*) 2000; **29**: 691-693
10 **Morrison RS**, Siu AL. Mortality from pneumonia and hip

fractures in patients with advanced dementia *JAMA* 2000; **284**: 2447-2448
11 **Nightingale S**, Holmes J, Mason J, House A. Psychiatric illness and mortality after hip fracture. *Lancet* 2001; **357**: 1264-1265
12 **Sato Y**, Iwamoto J, Honda Y. Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in Parkinson's disease. *Parkinsonism Relat Disord* 2011; **17**: 22-26
13 **Sato Y**, Honda Y, Kaji M, Asoh T, Hosokawa K, Kondo I, Satoh K. Amelioration of osteoporosis by menatetrenone in elderly female Parkinson's disease patients with vitamin D deficiency. *Bone* 2002; **31**: 114-118
14 **Sato Y**, Iwamoto J, Kanoko T, Satoh K. Alendronate and vitamin D2 for prevention of hip fracture in Parkinson's disease: a randomized controlled trial. *Mov Disord* 2006; **21**: 924-929
15 **Sato Y**, Honda Y, Iwamoto J. Risedronate and ergocalciferol prevent hip fracture in elderly men with Parkinson disease. *Neurology* 2007; **68**: 911-915
16 **Sato Y**, Iwamoto J, Honda Y. Once-weekly risedronate for prevention of hip fracture in women with Parkinson's disease: a randomised controlled trial. *J Neurol Neurosurg Psychiatry* 2011; **82**: 1390-1393
17 **Sato Y**, Inose M, Higuchi I, Higuchi F, Kondo I. Changes in the supporting muscles of the fractured hip in elderly women. *Bone* 2002; **30**: 325-330
18 **Bischoff-Ferrari HA**, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, Wong JB. Effect of Vitamin D on falls: a meta-analysis. *JAMA* 2004; **291**: 1999-2006
19 **Bischoff-Ferrari HA**, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA* 2005; **293**: 2257-2264
20 **Epstein S**. Is cortical bone hip? What determines cortical bone properties? *Bone* 2007; **41**: S3-S8
21 **Iwamoto J**, Sato Y, Takeda T, Matsumoto H. Hip fracture protection by alendronate treatment in postmenopausal women with osteoporosis: a review of the literature. *Clin Interv Aging* 2008; **3**: 483-489
22 **Beadle PC**. Sunlight, ozone and vitamin D. *Br J Dermatol* 1977; **97**: 585-591
23 **Lester E**, Skinner RK, Foo AY, Lund B, Sørensen OH. Serum 25-hydroxyvitamin D levels and vitamin D intake in healthy young adults in Britain and Denmark. *Scand J Clin Lab Invest* 1980; **40**: 145-150
24 **Sato Y**, Metoki N, Iwamoto J, Satoh K. Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in stroke patients. *Neurology* 2003; **61**: 338-342
25 **Szulc P**, Chapuy MC, Meunier PJ, Delmas PD. Serum undercarboxylated osteocalcin is a marker of the risk of hip fracture in elderly women. *J Clin Invest* 1993; **91**: 1769-1774
26 **Szulc P**, Chapuy MC, Meunier PJ, Delmas PD. Serum undercarboxylated osteocalcin is a marker of the risk of hip fracture: a three year follow-up study. *Bone* 1996; **18**: 487-488
27 **Vergnaud P**, Garnero P, Meunier PJ, Bréart G, Kamihagi K, Delmas PD. Undercarboxylated osteocalcin measured with a specific immunoassay predicts hip fracture in elderly women: the EPIDOS Study. *J Clin Endocrinol Metab* 1997; **82**: 719-724
28 **Iwamoto J**, Takeda T, Sato Y. Effects of vitamin K2 on osteoporosis. *Curr Pharm Des* 2004; **10**: 2557-2576
29 **Iwamoto J**, Takeda T, Sato Y. Effects of vitamin K2 on the development of osteopenia in rats as the models of osteoporosis. *Yonsei Med J* 2006; **47**: 157-166
30 **Knapen MH**, Schurgers LJ, Vermeer C. Vitamin K2 supplementation improves hip bone geometry and bone strength indices in postmenopausal women. *Osteoporos Int* 2007; **18**: 963-972
31 **Yaegashi Y**, Onoda T, Tanno K, Kuribayashi T, Sakata K, Orimo H. Association of hip fracture incidence and intake of calcium, magnesium, vitamin D, and vitamin K. *Eur J Epidemiol* 2008; **23**: 219-225
32 **Hochberg MC**, Greenspan S, Wasnich RD, Miller P, Thompson DE, Ross PD. Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. *J Clin Endocrinol Metab* 2002; **87**: 1586-1592

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