Effect of High-Dosage Cholecalciferol and Extended Physiotherapy on Complications After Hip Fracture

A Randomized Controlled Trial

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Background: Care of elderly patients after hip fracture is not well established.

Methods: We enrolled 173 patients with acute hip fracture who were 65 years or older (79.2% women; mean age, 84 years; 77.4% living at home). Using a factorial design, we randomly allocated patients to extended physiotherapy (PT) (supervised 60 min/d during acute care plus an unsupervised home program) vs standard PT (supervised 30 min/d during acute care plus no home program; single-blinded), and to cholecalciferol therapy, 2000 vs 800 IU/d (double-blinded). Primary outcome was rate of falls; secondary outcome was rate of hospital readmissions during the 12-month follow-up. All analyses included 173 individuals and used multivariate Poisson regression analyses.

Results: At baseline, 50.9% of participants had 25-hydroxyvitamin D levels of less than 12 ng/mL and 97.7% of less than 30 ng/mL. We documented 212 falls and 74 hospital readmissions. Because this was a factorial design trial, all analyses tested the main effect of each treatment while controlling for the other in 173 participants. Extended vs standard PT reduced the rate of falls by 25% (95% confidence interval [CI], −44% to −1%). Cholecalciferol treatment, 2000 vs 800 IU/d, did not reduce falls (28%; 95% CI, −4% to 68%), but reduced the rate of hospital readmissions by 39% (95% CI, −62% to −1%).

Conclusions: Extended PT was successful in reducing falls but not hospital readmissions, whereas cholecalciferol treatment, 2000 IU/d, was successful in reducing hospital readmission but not falls. Thus, the 2 strategies may be useful together because they address 2 different and important complications after hip fracture.

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By the ninth decade of life, 1 of every 3 women and 1 of every 6 men will have sustained a hip fracture.[1] The consequences are severe. In the first 12 months after the fracture, 10% fracture their other hip, 30% are readmitted to acute care, 50% are left with permanent functional disabilities, 25% require long-term care, and 10% to 25% die.[2-5] Despite the high frequency of adverse events, evidence to support specific interventions to reduce these outcomes is limited.[6]

Supplemental cholecalciferol (700-1000 IU/d) reduces falls[7] and nonvertebral fractures[8] in community-dwelling and institutionalized older individuals. Thus, patients with hip fracture may benefit from cholecalciferol supplementation, but may need a higher dose of cholecalciferol to correct their severe vitamin D deficiency.[9-11] Cholecalciferol may also reduce morbidity via multiple mechanisms.[12-14]

Secondary prevention may also include physiotherapy (PT) applied as an instructed unsupervised home program; several studies of older individuals found a reduction of falls with exercise.[15-17] However, the benefit of such a program has not been evaluated after acute hip fracture.

The goal of this randomized controlled trial was to determine the additive benefit of extended PT and cholecalciferol therapy, 2000 IU/d, on the rate of falls and hospital readmissions in the first 12 months after acute hip fracture.

METHODS

DESIGN OVERVIEW

In this 12-month trial, participants were randomized to PT (extended or standard) and to vitamin D_3 therapy (2000 or 800 IU/d; 800 IU/d

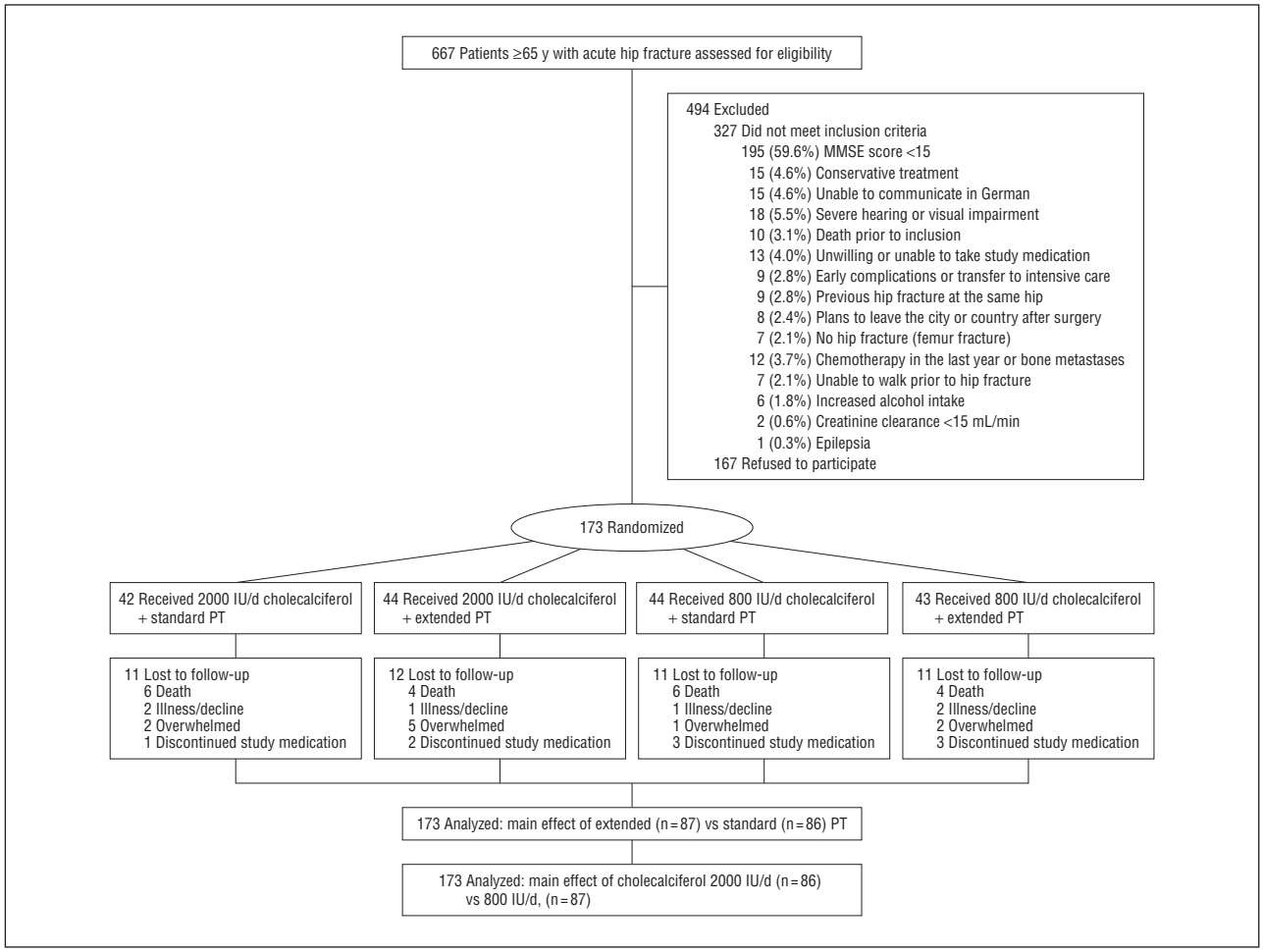

Figure. Randomization of participants in the study. MMSE indicates Mini-Mental State Examination; PT, physiotherapy.

was considered the standard of care) in a factorial design trial. The primary end point was the rate of falls. The secondary end point was health care utilization measured as the rate of hospital admissions.

SETTING AND PARTICIPANTS

We studied patients with acute hip fracture 65 years or older from a large hospital center (Triemli City Hospital). Participants had to reach a Folstein Mini-Mental State Examination score of at least 15,[18] have no prior hip fracture at the newly fractured hip, undergo surgical repair of the fracture, understand German, have no metastatic cancer or chemotherapy in the last year, have no severe visual or hearing impairment, have creatinine clearance of more than 15 mL/min (to convert to milliliters per second, multiply by 0.0167), be able to walk at least 3 m before their hip fracture, and have no kidney stone in the past 5 years, no hypercalcemia, and no primary hyperparathyroidism or sarcoidosis. Participants were advised to maintain their usual diets and to avoid taking calcium and cholecalciferol supplements on their own throughout the study.

SCREENING AND RANDOMIZATION

We prescreened all 667 patients with acute hip fracture 65 years or older admitted from January 1, 2005, through December 31, 2007. Of these, 327 did not meet our inclusion criteria (**Figure**). Of 341 patients eligible after prescreening, 173 agreed to participate. The prescreening and trial protocols were approved by the Kantonal Ethics Committee at the University of Zurich, and written informed consent was obtained from each participant.

Computer-based randomization was performed by the study statistician (E.J.O.). Randomization for the dosage of cholecalciferol was double-blinded, whereas randomization for PT was single-blinded (all study staff except the treating physiotherapist who instructed the home program were blinded to the PT treatment allocation).

INTERVENTIONS

Physiotherapy

Participants were randomly assigned to standard PT (30 min/d during acute care with no home program) or to extended PT. The extended PT program included an additional 30 minutes of home program instruction each day during acute care. The additional instructions prepared subjects for the home program, using the following simple components: standing on both legs and then standing on 1 leg while holding a handrail (simple balance component), pulling a rubber band while sitting for arm strength training, getting in and out of a chair, and going up and down stairs (functional mobility). At discharge, the extended PT group also received a leaflet that illustrated the home program with our recommendation to follow the home program for 30 minutes each day (all material available on request from the authors).

One physiotherapist conducted the home program instruction while another physiotherapist, blinded to treatment assignments, conducted all assessments of strength and function at baseline and at the 6- and 12-month follow-up visits. To maintain the blinding of our study staff to the PT group, we assessed adherence to the home program (at least once per week vs less) only at the 12-month follow-up visit or by telephone call.

Cholecalciferol Therapy

For breakfast and at bedtime, participants took a tablet containing 400 IU of cholecalciferol and 500 mg of elemental calcium as calcium carbonate (Nycomed, Wädenswil, Switzerland). Also, with breakfast, participants took a study capsule containing 1200 IU of cholecalciferol or placebo, identical in appearance and taste. The study capsules were prepared in a single batch (Streuli AG, Uznach, Switzerland); an assay confirmed that the dose was 1269 IU of cholecalciferol.

OUTCOMES AND FOLLOW-UP

Baseline assessments were performed after hip fracture surgery, during acute care (mean [SD], 4.2 [2.2] days after hip fracture surgery; range, 1-12 days). Clinical visits were at 6 and 12 months. Falls, fall-related injuries, and hospital readmissions were assessed by monthly telephone calls and a patient diary. In addition, a telephone hotline was provided to report these events at any time. Unique fall events were identified by comparing the date and circumstances of each report from different ascertainment methods. All admission records were reviewed by 3 blinded coinvestigators (H.A.B.-F., A.E., and N.J.M.) to determine the main cause of readmission.

Falls were defined as "unintentionally coming to rest on the ground, floor, or other lower level." Coming to rest against furniture or a wall was not counted as a fall.[19] The primary analysis included the total number of falls per person. We truncated the total number of falls for 1 person from 36 to 9, the next highest fall frequency observed. Comorbid conditions were assessed at baseline with the Charlson comorbidity index.[20] Functional assessment at baseline and 6 and 12 months included knee extensor and flexor strength for the leg undergoing operation and the other leg, grip strength, and the timed Up & Go test. All tests showed good reproducibility in an earlier trial of frail elderly individuals.[21]

Fasting venous blood was collected between 7 and 10 AM at baseline and the 6- and 12-month follow-up visit for measurement of levels of 25-hydroxyvitamin D (25[OH]D) (using a radioimmunoassay from Diasorin, Inc, Stillwater, Minnesota), calcium corrected for albumin, and creatinine. Creatinine clearance was calculated using the Cockcroft-Gault formula.[22]

STATISTICAL ANALYSES

All analyses were based on intent to treat and included 173 individuals. We used Poisson regression to evaluate the effect of extended PT compared with standard PT and the effect of 2000 vs 800 IU/d dosages of cholecalciferol on the rates of falling and hospital readmissions during the 12-month follow-up visit. The appropriateness of the Poisson model in terms of overdispersion was checked using the ratio of the model deviance to its degrees of freedom and found to be excellent for readmissions (1.03) and reasonable for falls (1.80). Because this was a factorial design trial, we tested and confirmed our assumption of no interaction between the 2 treatment strategies. Thus, all analyses test the main effect of each treatment while controlling for the other treatment strategy.

The multivariate analyses for rates of falls and hospital readmissions controlled for age in years, sex, baseline body mass index, baseline plasma 25(OH)D level, baseline height, living situation before the hip fracture (home, assisted living, or nursing home), and exposure time (days in the trial). To account for the reduced exposure time among patients who died or withdrew from the study, we used an offset in the Poisson regression for the number of days in the study.

For our predefined subgroup analyses comparing the rate of hospital readmissions due to fall-related injury, infection, and other causes, the Poisson regression controlled for trial design (both treatment strategies), living situation before the hip fracture (home, assisted living, or nursing home, to capture significant frailty), and exposure time (days in the trial), again using the offset for the number of days in the study. These adjustments were also used for the adjusted risk of death and new nursing home admission by treatment strategy. Because of the limited number of events in the subgroup analyses, it was not possible to include additional covariates in these regression models. To evaluate a benefit of extended PT and 2000 IU/d of vitamin D_3 on measured strength and functional mobility at 6 and 12 months, we used repeated-measures linear regression analyses controlling for baseline strength/function, time, age, sex, and body mass index. The mixed linear regression model included all of the other covariates listed, as well as the main effects of PT and the dose of vitamin D.

Analyses were conducted with SAS statistical software (version 9.1; SAS Institute Inc, Cary, North Carolina). All *P* values are 2 sided. Unless otherwise specified, data are expressed as mean (SD).

RESULTS

PATIENT CHARACTERISTICS AND STUDY ADHERENCE

The baseline characteristics of the 173 subjects by treatment group are shown in **Table 1**. Mean age was 84 (range, 65-99) years at randomization; 79.2% of subjects were women; and the mean Folstein Mini-Mental State Examination score was 24.7 (3.7). We documented 212 falls (154 by monthly telephone calls, 92 by patient diary, 65 by fall hotline, and 34 by other sources [several falls were reported by >1 method]) with a rate of 1.43 falls per observed patient-year and 74 hospital readmissions with a rate of 0.5 per observed patient-year. Mean follow-up (observation time) was 312 (129) days.

During the trial, 45 participants dropped out after a mean follow-up of 118 (112) days; of these, 20 died, 10 stopped for personal reasons (ie, they were overwhelmed or lost interest), 6 withdrew because of illness and overall decline, and 9 withdrew because they wanted to discontinue the study medication therapy. Subjects who discontinued their study medication therapy were encouraged to return for all subsequent follow-up evaluations. Patients with incomplete follow-up were included in all analyses for rates of falls and hospital readmission, controlling for observation time.

The reported adherence, assessed by monthly calls, was 92.2% for the combined cholecalciferol plus calcium and 93.6% for the study capsule containing 1200 IU cholecalciferol or placebo. The adherence-adjusted dosage of cholecalciferol correlated significantly with the mea-

Table 1. Baseline Characteristics of Study Participants According to Treatment Strategy[a]

	Treatment Strategy					
	Cholecalciferol Therapy			PT		
	2000 IU/d (n=86)	800 IU/d (n=87)	*P* Value	Extended (n=87)	Standard (n=86)	*P* Value
Women	68 (79)	69 (79)	.97	68 (78)	69 (80)	.74
Age, mean (SD), y	84.1 (7.0)	84.4 (6.8)	.78	83.4 (7.2)	85.1 (6.5)	.10
BMI, mean (SD)	24.2 (4.3)	24.2 (4.3)	.83	24.6 (4.5)	24.1 (4.2)	.40
Height, mean (SD), m	1.61 (0.09)	1.61 (0.08)	.82	1.61 (0.09)	1.61 (0.08)	.84
Living situation before hip fracture						
Home	69 (80)	65 (75)		72 (83)	62 (72)	
Assisted living	15 (17)	14 (16)	.15	10 (11)	19 (22)	.17
Nursing home	2 (2)	8 (9)		5 (6)	5 (6)	
Baseline 25(OH)D level, mean (SD), ng/mL	13.2 (8.1)	12.3 (7.7)		14.0 (8.8)	11.5 (6.8)	
<12	42 (49)	46 (53)		41 (47)	47 (55)	
12-19	24 (28)	27 (31)	.41	24 (28)	27 (31)	.03
20-30	18 (21)	12 (14)		18 (21)	12 (14)	
>30	2 (2)	2 (2)		4 (5)	0	
Charlson comorbidity index, mean (SD)	2.6 (1.8)	3.0 (2.0)	.22	2.6 (1.8)	3.0 (2.0)	.12
Glomerular filtration rate, mean (SD), mL/min	53.0 (24.7)	51.7 (19.8)	.70	53.9 (24.0)	50.7 (20.6)	.35

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of the height in meters); 25(OH)D, 25-hydroxyvitamin D; PT, physiotherapy.

SI conversion factor: To convert 25(OH)D to nanomoles per liter, multiply by 2.496.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

sured 25(OH)D levels at the 6-month (correlation coefficient, 0.48; $P<.001$; 117 participants) and 12-month (correlation coefficient, 0.44; $P<.001$; 116 participants) follow-up visits.

Mean days of PT during acute care were 7.6 (95% confidence interval [CI], 6.3-8.9) in the standard group and 7.2 (95% CI, 6.4-8.0) in the extended PT group; total minutes of PT were 176 (95% CI, 144-208; 23 min/d) with standard PT and 292 (95% CI, 259-326; 41 min/d) with extended PT. Sixty-five of 87 persons randomized to extended PT were reached for the 12-month visit or a telephone call. Of those, 45 (69%) reported having performed the home program at least once a week; of these, 4 (9%) answered that the home program did not make them stronger or more mobile, 24 (53%) answered that the program made them somewhat stronger and somewhat more mobile, and 17 (38%) answered that the home program made them a lot stronger and a lot more mobile.

RATE OF FALLS

We documented 212 falls in 92 participants (38 [41%] fell once, 24 [26%] fell twice, 17 [18%] fell 3 times, and 13 [14%] fell >3 times). Extended PT reduced the rate of falls significantly by 25% (adjusted relative rate difference, –25%; 95% CI, –44% to –1%; **Table 2**). In an efficacy analysis based on participation in the home program at least once a week (n=45), the rate of falls was reduced by 36% (adjusted relative rate difference, –36%; 95% CI, –55% to –9%) compared with individuals who did not participate in the home program at least once a week or were randomized to standard PT (n=128).

Although there was no significant difference in functional outcomes by PT group assignment, persons who engaged in the home program at least once a week performed significantly better in 3 of 4 functional tests measured at the 6- and 12-month follow-up visits compared with those who did not engage in the home program or were randomized to standard PT, independent of their baseline strength/function, age, sex, and body mass index. We found an 8% higher knee extensor strength ($P=.02$), a 37% higher grip strength ($P=.004$), and a 39% better functional mobility (quicker performance in the timed Up & Go test; $P=.047$), but no significant benefit for knee flexor strength (–3%; $P=.96$).

The 2000- vs 800-IU/d dosages of cholecalciferol did not reduce the rate of falls or improve strength or function. The nonsignificant increase in the overall rate of falls in the 2000-IU/d group (Table 2) was driven to a large extent by patients with hip fracture who experienced multiple falls; however, even when we restricted the comparison to those who fell and did not fall, there was no benefit of the higher dosage of cholecalciferol.

RATE OF HOSPITAL READMISSION

We documented 74 hospital readmissions in 54 of the original 173 participants (38 [70%] had 1 readmission, 12 [22%] had 2 readmissions, and 4 [7%] had 3 readmissions). The 2000- vs 800-IU/d dosage of cholecalciferol reduced the rate of hospital readmissions significantly by 39% (adjusted relative rate difference, –39%; 95% CI, –62% to –1%), whereas extended vs standard PT did not (Table 2). In an efficacy analysis based on the multivariate analysis for estimated daily cholecalciferol dose (dose × reported adherence in monthly telephone calls), the rate of hospital readmissions was reduced by 55% by the 2000-IU/d dosage of cholecalciferol (adjusted relative rate difference, –55%; 95% CI, –79% to –2%). As shown in **Table 3**, the overall reduction of the rate of hospital readmissions with the 2000-IU/d dosage of cholecalciferol was primarily driven by fewer readmissions due to

Table 2. Rates of Falls and Hospital Readmission by Treatment Strategy[a]

	Treatment Strategy							
	Cholecalciferol Therapy				PT			
	2000 IU/d (n=86)	800 IU/d (n=87)	Crude Relative Rate Difference (95% CI)	Adjusted Relative Rate Difference (95% CI)	Extended (n=87)	Standard (n=86)	Crude Relative Rate Difference (95% CI)	Adjusted Relative Rate Difference (95% CI)
Primary end point								
Rate of falls per observed patient-year	1.63	1.25	30 (–1 to 70)	28 (–4 to 68)	1.21	1.66	–28 (–45 to –5)	–25 (–44 to –1)
Secondary end point								
Rate of hospital readmission per observed patient-year	0.40	0.59	–35 (–59 to 5)	–39 (–62 to –1)	0.50	0.51	1 (–37 to 59)	7 (–33 to 73)

Abbreviations: CI, confidence interval; PT, physiotherapy.
[a]Effect sizes are based on Poisson regression models, controlling for treatment strategies, sex, age, living situation before the hip fracture (home, assisted living, or nursing home), Charlson comorbidity index, body mass index, height, baseline 25-hydroxyvitamin D levels, and exposure time (days in the trial) in the multivariate analyses. The crude relative rate difference controls for treatment strategies only.

Table 3. Hospital Readmission After Hip Fracture by Reason and Treatment Strategy[a]

	Treatment Strategy					
	Cholecalciferol Therapy			PT		
No. of Hospital Readmissions, Reason	2000 IU/d (n=86)	800 IU/d (n=87)	Adjusted Relative Rate Difference (95% CI)	Extended (n=87)	Standard (n=86)	Adjusted Relative Rate Difference (95% CI)
Fall-related injury	7	18	–60 (–83 to –3)	9	16	–47 (–77 to 20)
Any nonvertebral fracture	7	15		7	15	
Hip fracture	3	6		2	7	
Soft-tissue injury	0	3		2	1	
Infection	1	10	–90 (–99 to –13)	7	4	102 (–42 to 605)
Hip prosthesis infection	1	2		1	2	
Pneumonia	0	1		1	0	
Bronchitis	0	1		1	0	
Colitis	0	2		2	0	
Sepsis	0	3		1	2	
Infected indwelling catheter	0	1		1	0	
Other	18	13	45 (–29 to 198)	16	15	–3 (–52 to 96)

Abbreviations: CI, confidence interval; PT, physiotherapy.
[a]The adjusted relative rate difference is based on Poisson regression analyses, controlling for trial design (the other treatment strategy), living situation before the hip fracture, and exposure time (days in the trial). With respect to number of patients with these events, 7 patients were readmitted with fall-related injuries in the 2000-IU/d dosage group vs 13 in the 800-IU/d dosage group, 8 in the extended PT group, and 12 in the standard PT group. One patient was readmitted with infection in the 2000-IU/d dosage group vs 7 in the 800-IU/d dosage group, 6 in the extended PT group, and 2 in the standard PT group. All subsequent refractures were treated in inpatient care: the rate of refracture per observed patient-year was 0.10 in the 2000-IU/d group (n=7) compared with 0.19 in the 800-IU/d group (n=15) and 0.09 in the extended PT group (n=7) compared with 0.21 in the standard PT group (n=15). For refractures, the adjusted relative rate difference was –52% for the 2000-IU/d vs 800-IU/d dosage group (95% CI, –0.80% to 19%; P=.11) and –56% for the extended vs standard PT group (–82% to 9%; P=.08).

fall-related injury (–60%) and by fewer infections (–90%). Extended PT also reduced admissions due to fall-related injury (–47%), but not significantly.

25(OH)D LEVELS

Participants allocated to 2000-IU/d dosage of cholecalciferol achieved 17% higher 25(OH)D levels at the 6-month follow-up and 21% higher levels at the 12-month follow-up ($P<.001$; **Table 4**). Severe vitamin D deficiency (25[OH]D level <12 ng/mL) (to convert to nanomoles per liter, multiply by 2.496) was eradicated by both dosages, whereas, at 12 months, 42 (70%) of the participants in the 800-IU/d group and 54 (93%) in the 2000-IU/d group reached desirable levels of at least 30 ng/mL.

SAFETY, REFRACTURE, AND MORTALITY

In the 800-IU/d group, mean albumin-corrected serum calcium levels were 9.0 (0.5) mg/dL at baseline, 9.6 (0.5) mg/dL at 7 to 10 days after treatment start, and 9.5 (0.5) mg/dL at the 6-month follow-up visit (to convert to micromoles per liter, multiply by 0.25). In the 2000-IU/d group, albumin-corrected serum calcium levels were 9.0 (0.7) mg/dL at baseline, 9.4 (0.5) mg/dL at 7 to 10 days after treatment start, and 9.4 (0.5) mg/dL at the 6-month follow-up visit. There were 3 cases of mild hypercalcemia (defined as a level between 10.8 and 11.6 mg/dL) at 7 to 10 days of follow-up (2 with 800 IU/d, both with 10.8 mg/dL, and 1 with 2000 IU/d at 10.9 mg/dL). There were 3 cases of mild hypercalcemia at the 6-month follow-up (1 with 800 IU/d at 11.6 mg/dL, and 2 with 2000

Table 4. Percentage of Patients With Hip Fracture by 25-Hydroxyvitamin D (25[OH]D) Category and Dosage of Cholecalciferol at Baseline and the 6- and 12-Month Follow-up Visits[a]

Dosage Group	25(OH)D Level, Mean (SD), ng/mL	25(OH)D Level, ng/mL			
		<12	12-19	20-30	>30
Baseline					
800 IU/d (n=87)	12.1 (8.0)	46 (53)	18 (21)	11 (13)	2 (2)
2000 IU/d (n=86)	13.1 (8.2)	43 (50)	23 (27)	18 (21)	2 (2)
P value	.41				
6-mo follow-up					
800 IU/d (n=67)	37.7 (9.6)	0	3 (4)	10 (15)	54 (81)
2000 IU/d (n=62)	45.4 (8.7)	0	0	2 (3)	60 (97)
P value	<.001				
12-mo follow-up					
800 IU/d (n=60)	35.4 (10.1)	1 (2)	2 (3)	15 (25)	42 (70)
2000 IU/d (n=58)	44.7 (10.4)	0	0	4 (7)	54 (93)
P value	<.001				

SI conversion factor: To convert 25(OH)D to nanomoles per liter, multiply by 2.496.
[a]Unless otherwise indicated, data are expressed as the number (percentage) of patients.

IU/d at 10.8 and 11.2 mg/dL). Of these, 2 of 3 returned to normal levels with treatment at 12 months of follow-up. Creatinine clearance did not differ significantly between groups at baseline or at 7 to 10 days, or 6 and 12 months of follow-up. There was no report of nephrolithiasis throughout the trial period.

The rate of subsequent refracture is presented in Table 3. The rate of death per observed patient-year was 0.14 for the 2000-IU/d group (n=10) and 0.13 for the 800-IU/d group (n=10), 0.12 for extended PT (n=9), and 0.15 for standard PT (n=11). The adjusted odds ratio of death was 0.20 for the 2000- vs 800-IU/d group (95% CI, 0.02-2.71; *P*=.23) and 0.26 for extended vs standard PT (0.02-3.66; *P*=.32).

The rate of new nursing home admissions per observed patient-year was 0.30 for the 2000-IU/d group (n=17), 0.38 for the 800-IU/d group (n=22), 0.34 for extended PT (n=21), and 0.34 for standard PT (n=18). The adjusted odds ratio of new nursing home admission was 0.66 for the 2000- vs 800-IU/d group (95% CI, 0.31-1.41; *P*=.28) and 1.02 for extended vs standard PT (2.18-0.48; *P*=.95).

COMMENT

Our results show a differential benefit of extended PT and a dosage of 2000 IU/d of vitamin D_3 in the first year after hip fracture. The easy-to-implement PT home program reduced the rate of falls by 25% compared with standard PT but did not reduce hospital readmission, whereas 2000 IU/d of cholecalciferol reduced the rate of hospital readmissions by 39% compared with 800 IU/d of cholecalciferol but did not reduce the rate of falls.

The benefit of fall reduction with our extended PT program is consistent with a randomized trial by Campbell and colleagues,[17] which showed a reduction in falls among community-dwelling elderly women 80 years or older with an unsupervised home program. The gain in strength and functional mobility found in participants adherent to the home program provides mechanistic evidence, and their more pronounced fall reduction of 36% compared with 25% in the intent-to-treat analysis indicates the efficacy of the program. Consistent with the overall reduction in the rate of falls with extended PT, there was a suggestion that extended PT may reduce the rate of hospital readmissions due to fall-related injuries, although this was not significant.

To our knowledge, this is the first randomized controlled trial to test and show a benefit of cholecalciferol supplementation on hospital readmissions after hip fracture. In a recent meta-analysis of double-blind randomized controlled trials, antifracture efficacy was reported to be dose-dependent and enhanced with a higher dosage of vitamin D supplementation or a serum 25(OH)D level beyond 30 ng/mL,[8] which may explain the observed benefit for fall-related injuries, primarily refracture, leading to hospital readmission with the 2000 compared with 800-IU/d dosage of cholecalciferol. Furthermore, the emerging recognition of the role of cholecalciferol in the immune response to infectious agents, such as tuberculous bacteria[23] or viral and bacterial infections of the respiratory tract,[24,25] could explain the reduction in infections that lead to hospital readmission with the 2000-IU/d dosage of cholecalciferol. However, these findings are based on small numbers in the subgroup analyses for hospital readmission and need confirmation in a larger trial.

Although we expected cholecalciferol supplementation to reduce the overall rate of falls, as shown in several randomized trials among institutionalized and community-dwelling older individuals and summarized in a recent meta-analysis,[8] this could not be confirmed in patients with acute hip fracture for comparison of 2000- and 800-IU/d dosages of cholecalciferol. One explanation may be that most of the benefit of cholecalciferol on muscle strength and fall prevention is achieved at a dose of 800 IU/d,[8] which was the experimental dosage in earlier trials. Also, the most recent meta-analysis of double-blind randomized controlled trials suggested a fall-prevention threshold of 24 ng/mL, a level that most people achieve with a supplement dosage of 800 IU/d.[7] Alternatively, frailty in our study was greater than in other

double-blinded trials with cholecalciferol, which may have overridden the benefit of cholecalciferol. However, our subgroup analyses suggested a lower rate of hospital readmissions due to fall-related injuries, primarily refractures, with the 2000- vs 800-IU/d dosage of cholecalciferol. Thus, a higher dosage of cholecalciferol supplement may be important for the prevention of falls with injury, which is consistent with the higher fracture prevention threshold of 30 ng/mL of 25(OH)D suggested in a recent meta-analysis.[8] In our trial, more than 90% of participants randomized to 2000-IU/d dosage of cholecalciferol reached a threshold of at least 30 ng/mL at 6 and 12 months of treatment.

There are several strengths of this trial. With the high level of frailty after acute hip fracture, our trial was powered for the end points investigated despite its moderate size, and adverse event rates were consistent with the literature.[2-5] Furthermore, the trial was designed to compare 2 optimized treatment strategies against current treatment strategies in a largely unselected sample of patients with hip fractures. Moreover, the efficacy analyses showed an enhanced treatment effect for the rate of falls with adherence to the extended PT program and for hospital readmissions by received dose of cholecalciferol, which would be expected if there is a true treatment effect.

Because clinical interventions in elderly hip fracture patients are not well established, our findings may have important clinical implications. The interventions are practical, well tolerated in elderly patients with hip fractures and multiple comorbidities, and relatively low in cost. The effect sizes demonstrated on falls and hospital readmission are clinically meaningful, especially if the frequency and severity of the events prevented are considered. Finally, our subgroup findings of reduced hospital readmission due to fall-related injury, primarily refracture, and infections may stimulate future research to test these end points in a larger trial.

In conclusion, extended PT and supplementation with cholecalciferol, 2000 IU/d, had differential benefits in care after hip fracture. Extended PT reduced falls but not hospital readmissions, and supplementation with 2000 IU/d of cholecalciferol reduced hospital readmission but not falls. Thus, the 2 strategies may be useful together because they address 2 different and important complications after hip fracture.

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REFERENCES

1. Birge SJ, Morrow-Howell N, Proctor EK. Hip fracture. *Clin Geriatr Med*. 1994;10(4):589-609.
2. Giusti A, Barone A, Razzano M, Pizzonia M, Oliveri M, Pioli G. Predictors of hospital readmission in a cohort of 236 elderly discharged after surgical repair of hip fracture: one-year follow-up. *Aging Clin Exp Res*. 2008;20(3):253-259.
3. Magaziner J, Hawkes W, Hebel JR, et al. Recovery from hip fracture in eight areas of function. *J Gerontol A Biol Sci Med Sci*. 2000;55(9):M498-M507.
4. Cummings SR, Kelsey JL, Nevitt MC, O'Dowd KJ. Epidemiology of osteoporosis and osteoporotic fractures. *Epidemiol Rev*. 1985;7:178-208.
5. Boockvar KS, Halm EA, Litke A, et al. Hospital readmissions after hospital discharge for hip fracture: surgical and nonsurgical causes and effect on outcomes. *J Am Geriatr Soc*. 2003;51(3):399-403.
6. Anders RL, Ornellas EM. Acute management of patients with hip fracture: a research literature review. *Orthop Nurs*. 1997;16(2):31-46.
7. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials *BMJ*. 2009;339:b3692. doi:10.1136/bmj.b3692.
8. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2009;169(6):551-561.
9. LeBoff MS, Kohlmeier L, Hurwitz S, Franklin J, Wright J, Glowacki J. Occult vitamin D deficiency in postmenopausal US women with acute hip fracture. *JAMA*. 1999;281(16):1505-1511.

10. Bischoff-Ferrari HA, Can U, Staehelin HB, et al. Severe vitamin D deficiency in Swiss hip fracture patients. *Bone*. 2008;42(3):597-602.
11. Heaney RP. The vitamin D requirement in health and disease. *J Steroid Biochem Mol Biol*. 2005;97(1-2):13-19.
12. Dobnig H, Pilz S, Scharnagl H, et al. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med*. 2008;168(12):1340-1349.
13. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2007;167(16):1730-1737.
14. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr*. 2004;79(3):362-371.
15. Province MA, Hadley EC, Hornbrook MC, et al. The effects of exercise on falls in elderly patients: a preplanned meta-analysis of the FICSIT Trials: Frailty and Injuries: Cooperative Studies of Intervention Techniques. *JAMA*. 1995;273(17):1341-1347.
16. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev*. 2009;(2):CD007146.
17. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Tilyard MW, Buchner DM. Randomised controlled trial of a general practice programme of home based exercise to prevent falls in elderly women. *BMJ*. 1997;315(7115):1065-1069.
18. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
19. Buchner DM, Hornbrook MC, Kutner NG, et al. Development of the common data base for the FICSIT trials. *J Am Geriatr Soc*. 1993;41(3):297-308.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
21. Bischoff HA, Stähelin HB, Dick W, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *J Bone Miner Res*. 2003;18(2):343-351.
22. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
23. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D–mediated human antimicrobial response. *Science*. 2006;311(5768):1770-1773.
24. Cannell JJ, Vieth R, Umhau JC, et al. Epidemic influenza and vitamin D. *Epidemiol Infect*. 2006;134(6):1129-1140.
25. Laaksi I, Ruohola JP, Tuohimaa P, et al. An association of serum vitamin D concentrations <40 nmol/L with acute respiratory tract infection in young Finnish men. *Am J Clin Nutr*. 2007;86(3):714-717.

Images From Our Readers

Wheels in front of window in Rome, Italy.

Courtesy of: Steven A. Yarows, MD, Chelsea Internal Medicine, Chelsea, Michigan.