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The effects of calcitriol on falls and fractures and physical performance tests☆

J.C. Gallagher*

Bone Metabolism Unit, Creighton University Medical Center, 601 N. 30th Street (Suite 6718), Omaha, NE 68131, USA

Abstract

There is an increase in the incidence of falls with aging and about 10% of falls lead to fractures. Nearly all hip fractures are due to falls and hip fractures are the most severe of the osteoporotic fractures because they lead to a 20% mortality rate and a loss of independent living in 50% of cases. Although there are multiple factors associated with falls, our interest is the role that vitamin D metabolism plays in the pathogenesis of falls. Recent clinical trials show that both vitamin D and the metabolite calcitriol reduce the number of falls by 30–40% in elderly subjects. This should also reduce the number of fractures. In European studies, the decrease in falls could be attributed to an improvement in the muscle weakness that often accompanies vitamin D deficiency. However, in the studies using calcitriol there was no vitamin D deficiency, so the mechanism of its efficacy is less clear. It could be due to increased muscle strength, an improvement in the neurological control of balance or both. Understanding these mechanisms would allow us to search for analogs of vitamin D that act more selectively on muscle and on the central nervous system.

Keywords: Vitamin D calcitriol; Falls fractures; Physical performance tests

1. Introduction

Elderly people fall more often as they age. Falls occur in 30% of people over the age of 65 years and in 50% of people over age 80 years [1–3]. Increased falling is associated with subsequent admission to a nursing home [4]. About 20% of fall incidents require medical attention, and approximately 10% result in fractures [1,4–9]. About 50% of osteoporotic fractures are non-vertebral, and falls appear to be the biggest contributor to a non-vertebral fracture [10]. The most serious fracture due to a fall is hip fracture because it results in a mortality of 15–20% of patients and as many as 50% of hip fracture patients are so physically impaired that they never leave the nursing homes. There are several risk factors for falls in elderly people such as poor general health, diabetes, poor vision, urinary incontinence, a previous history of stroke, Parkinson's disease, dementia, poor cognitive function, depression, poor balance, decreased muscle strength, difficulty with the activities of daily living, medication use (particularly sedatives and anticonvulsants) and environmental obstacles and barriers [1]. Some of these risk factors are modifiable. A meta-analysis of several studies showed that different types of interventions could reduce the number of falls and multiple targeted interventions were shown to reduce the incidence of falls by about 10% [11]. In the present double blind randomized trial we examined prospectively the effect of calcitriol or estrogen therapy on bone mineral density and the incidence of falls and fractures.

2. Materials and methods

489 subjects were randomly assigned to one of the following four groups: conjugated equine estrogens (Premarin) 0.625 mg daily plus medroxyprogesterone acetate (Provera) 2.5 mg daily (HT); calcitriol (Rocaltrol) 0.25 μg twice daily; the combination of HT plus calcitriol; or placebo. Hysterectomized women ($n = 290$) assigned to estrogen were not given the progestin, but received estrogen alone (ET) [12]. Calcium intake was maintained at or below 1000 mg per day. On entry into the study, women underwent the following; medical history, physical examination, 7-day dietary history, after randomization, subjects came in at 6 and 12 weeks, then every 6 months for the duration of the 3 years. At each 6-month visit, tests were performed of bone mineral density (BMD) of spine and hip (DPXL scanner, Lunar Corp. Radiation, Madison, WI) and urine

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* Tel.: +1-402-280-4518; fax: +1-402-280-4517.
E-mail address: jcg@creighton.edu (J.C. Gallagher).

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and serum calcium. At each visit data was collected on any falls and fractures. At annual intervals women underwent physical performance measurements of grip strength, timed rising after five rises, timed walk over 5 m at normal and fast speed. Subjects were dispensed medication every 6 months, and all returned pills were counted at each 6-month visit in order to estimate compliance for that time period. At baseline and end of study, a fasting blood sample was collected for measurement of serum parathyroid hormone, 25 hydroxyvitamin D (25OHD), 1,25-dihydroxyvitamin D and osteocalcin and urine N telopeptides.

Serum and urine calcium and creatinine were measured on a Nova Nucleus. Serum osteocalcin was measured with the immunoradiometric assay (Incstar, Stillwater, MN), serum parathyroid hormone was measured by immunometric assay (Nichols Institute, Capistrano, CA), and serum 25 hydroxyvitamin D (25OHD) and 1,25-dihydroxyvitamin D as previously described [12]. Measurements of serum 25OHD by protein binding assay were cross-checked against direct HPLC measurements (Shimadsu) [13]. Urine N telopeptides were measured by an Elisa assay (Incstar) [13]. Data was collected prospectively by an interview-administered questionnaire on the incidence of falls and fractures at each visit, 6 and 12 weeks, and 6, 12, 18, 24, 30 and 36 months. The exact date of the fall was not ascertained at the time of the scheduled visit. All fractures were confirmed from X-ray reports. Lateral radiographs of the spine were performed at baseline and end of study; morphometric measurements on the vertebrae were performed to assess the presence of baseline fractures and the incidence of new fractures.

2.1. Statistical methods

The study assigned subjects to treatment groups using simple randomization stratified on hysterectomy status. Since the study hypotheses compared each of the three treatment groups to placebo, analyses corresponded to a four-group design rather than a factorial design. The data analyzed was based on the women who came in for final study visit even if they had discontinued medication. The level of significance was always 0.05, including the overall level when conducting multiple comparisons. Multiple comparisons, when performed, were handled by contrasts. The statistical package SAS (SAS Inst. Inc., Cary, NC, USA) was used in all analyses. The occurrence of falls was analyzed using recurrent event analysis. Because falls were ascertained at regular visits, the exact times of falls were not known, so homogeneity of the counting process over time could not be assessed directly. To compare the treatment groups on the rate of occurrence of falls over time, we used a homogeneous Poisson regression model [14] estimated with the SAS GENMOD procedure. The cumulative number of falls was modeled as a function of treatment group adjusted for the following covariates measured at baseline: age, BMI, serum 25 hydroxyvitamin D, 1,25-dihydroxyvitamin D, smoking, and caffeine [15].

The falls data were analyzed in two different ways in order to answer two different questions. The first question was how treatment affects the number of fallers. The second question was whether treatment affects the 36-month cumulative number of falls using the SAS procedure GENMOD with type 3 analysis. The Bonferroni correction was applied for comparisons of treatment versus placebo.

3. Results

The mean age of the women was 72 years at baseline and 75 years at the end of study. Mean serum 25OHD was 80 nmol/L (31 ng/ml), mean serum PTH was 37 pg/ml (normal <60). The effects of the therapy on BMD have previously been described [12].

The cumulative number of **fallers** was 64% in the placebo group versus 50% on calcitriol ($P < 0.0382$), 58% on ET/HT and 57% on ET/HT + calcitriol. Because of the multiple comparisons test the difference between placebo and calcitriol was not significant.

However, the incidence rate of **falls** averaged over 3 years was 0.43 on placebo versus 0.27 on calcitriol ($P = 0.0015$) which is significant after the multiple comparisons test. This is a reduction of 38%. The fall incidence rate was 0.39 on ET/HT and 0.35 on ET/HT + calcitriol and was not different from placebo. The difference between the calcitriol and placebo treated groups was already apparent at the end of the first year.

The incidence of all non vertebral fractures was 10.7% in the placebo group versus 4.9% on calcitriol ($P < 0.08$). The incidence was 11.9% in the ET/HT group and 7.8% on ET/HT + calcitriol.

The incidence of fractures due to falls was 7% on placebo, 4.6% on calcitriol, 11.7% in the ET/HT group and 4.8% on ET/HT + calcitriol. If the data were combined for the two groups on calcitriol there was a near significant difference ($P = 0.0528$) between the calcitriol groups compared to the two groups not on calcitriol (placebo and ET/HT).

The effects of calcitriol on physical performance tests are shown in Fig. 1. In all women physical performance declined with age but the decline was less in the calcitriol-treated group compared to placebo for the timed rising ($P < 0.1$) and timed walk ($P < 0.1$). Comparisons also were made between three groups, ‘no fallers’, ‘fallers’ and ‘fallers who fracture’. At baseline there were no differences between the ‘no fallers’ and the ‘fallers’, however, in the group that later fall and fracture there were lower physical activity scores, lower grip strength, slower timed rising, and slower walking speed compared to the other two groups.

4. Discussion

The results of this study raise questions about the present approach to fracture prevention in the elderly which focuses on the effects of pharmacological agents that increase bone

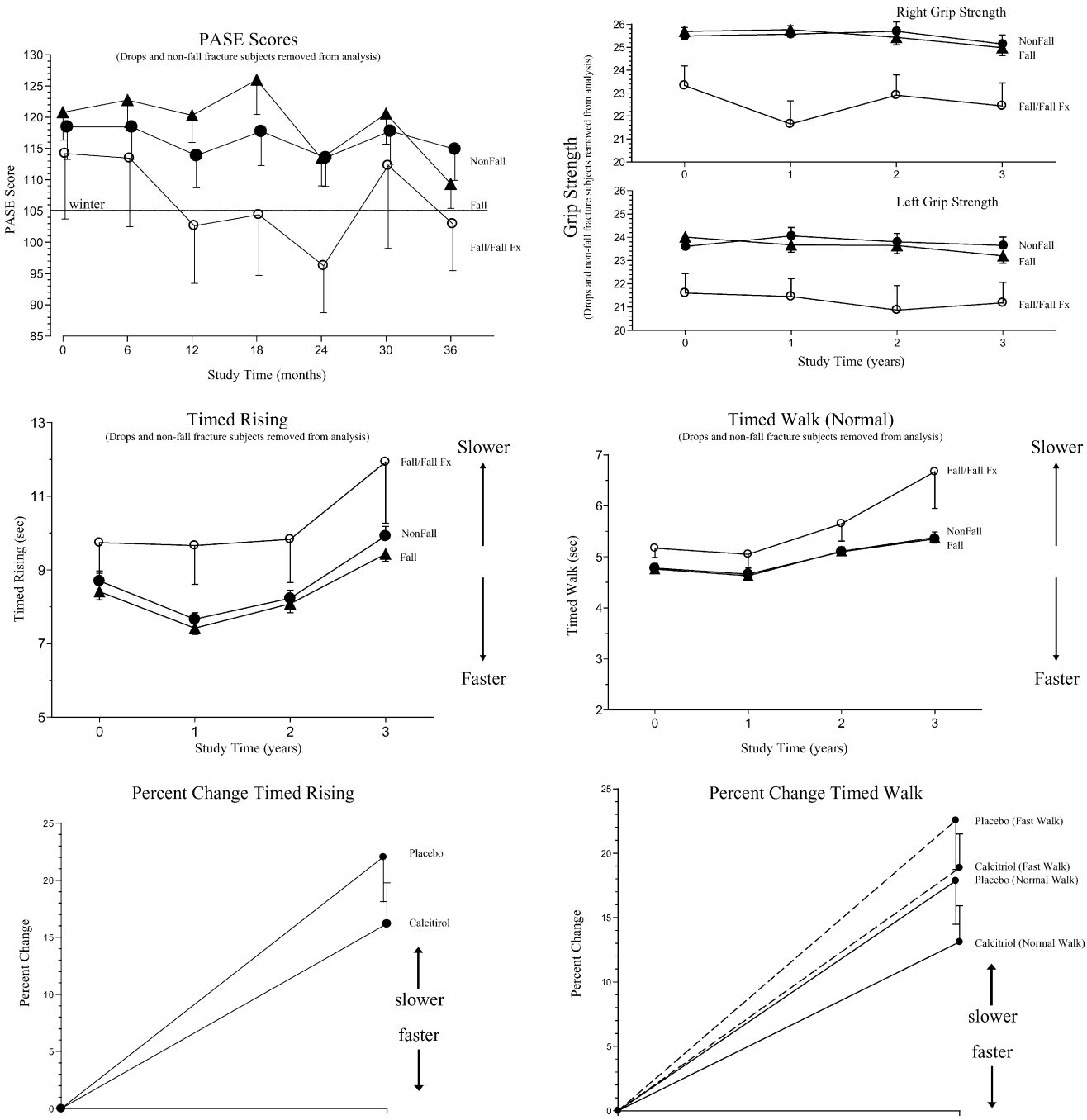

Fig. 1. Physical activity, grip strength, walking speed, timed rising in groups—falls, no falls, and falls/fractures. Effect of calcitriol or placebo on timed rising and timed walk.

mineral density (BMD). An analysis of the MORE trial showed that an increase in BMD could account for only 4% of the reduction in vertebral fractures [16]. Another analysis of all the large osteoporosis trials showed that only 16% of the decrease in vertebral fracture reduction could be accounted for by an increase in BMD [17]. It is now suggested that an improvement in bone quality is the main effect of bone active drugs. Still these analyses ignore the effect of falls on fracture rates although nearly all non vertebral fractures are due to falls. This may explain why there is no effect of raloxifene or alendronate on non vertebral fractures. A post hoc analysis later showed that alendronate only reduces non vertebral fractures in patients with low femoral neck density which we found in this study to be an independent risk factor for falls [18]. Another reason why therapy may not reduce non vertebral fractures is that the increase in BMD in peripheral bone is much smaller (1–2%) than occurs in the spine [19]. Thus, it may be more valuable to focus on the role of reducing falls as a way to reduce non vertebral fractures. Because of the increased development of

osteoporosis with age as well as the increased incidence of falls in the elderly, it is likely that the number of fall-related osteoporotic fractures also increase with age.

The results from this study suggest that the use of the vitamin D metabolite calcitriol can prevent falls and fall related fractures. Moreover, there was a trend toward reduced fall fracture incidence in both of the groups receiving calcitriol compared to ET/HT.

There is conflicting data on the use of simple vitamin D in the effect on the incidence of falls. Pfeifer et al. compared the effect of vitamin D (800 IU) and calcium (1200 mg) daily versus calcium 1200 mg alone in 148 healthy women aged 70 years or older [20]. Subjects were treated for several weeks, but over the next year 28% of the group on calcium versus 16% on vitamin D experienced a fall. This study also demonstrated an improvement in body sway in the vitamin D group, suggesting that vitamin D may improve postural stability. Another study involved 122 elderly women in a long-stay geriatric health center [21]. Falls were recorded for a 6-week period, and then subjects were randomized to either 1200 mg calcium and 800 IU vitamin D or 1200 mg calcium alone. The number of falls during the 12-week pre-treatment period (22 in the vitamin D plus calcium and 20 in the calcium group) were compared with those after treatment. Women treated with vitamin D and calcium experienced 25 falls in comparison to 55 falls in the calcium alone group, a 49% reduction. In both of these studies, there was evidence of moderately severe vitamin D deficiency (serum 25OHD ∼12 ng/ml or 30 nmol/l) and the authors postulated that it was the correction of muscle weakness due to vitamin D deficiency that decreased the fall incidence. In fact, there are studies that demonstrate an association between age-related decline in muscle strength and vitamin D deficiency [22]. The effect of vitamin D on fractures shows variability. Studies by Chapuy et al. [23] in 3270 women showed a reduction in fractures but patients were severely vitamin D deficient (serum 25OHD 14 ng/ml). Another study evaluated the effects of 3 years of supplementation with calcium and vitamin D 600 IU on BMD and in the incidence of non vertebral fracture [24]. In 176 men and 213 women (all >65 years) treatment produced a significant decrease ($P = 0.02$) in non vertebral fractures. In a placebo controlled trial of 2686 subjects, 100,000 IU of vitamin D3 every 4 months reduced fractures by 22% ($P < 0.04$) [25]. But in two other large studies of about 3000 patients, vitamin D was not shown to reduce fractures [26,27].

In our study the explanation for the decrease in falls on calcitriol is not so obvious since there was no vitamin D deficiency. Both muscle and the brain contain receptors for 1,25-dihydroxyvitamin D. One would have to postulate that calcitriol produces an improvement in muscle function or central nervous system function affecting balance. One explanation is that both calcitriol and vitamin D through its conversion to 1,25-dihydroxyvitamin D increases receptor activity in muscle and brain since 1,25-dihydroxyvitamin D is known to upregulate its own receptor.

Other strategies to reduce falls have included various exercise regimens. A review of pooled data from trials of exercise alone or exercise with behavioral/environmental interventions showed that exercise was not effective in reducing falls [11]. One study included in this review was a meta-analysis [28] reviewed seven studies that evaluated exercise alone or in concert with other interventions. Exercise resulted in a significant reduction in the time to a fall (incidence ratio 0.90; 95% CI 0.81–0.98) but not in time to an injurious fall (incidence ratio 0.83; 95% CI 0.70–0.98). One type of exercise has a positive impact on falls. A 15-week program of Tai Chi, which combines slow movements with strength training and postural stability improvement, was associated with a reduced risk of falling of 0.51 (95% CI 0.41–1.09) in comparison to controls [29].

Several factors that contribute to falls may be unresponsive to drug therapy [30]. These include urge incontinence, medications that impair cognition such as analgesics, psychotropics, sedatives or medications that induce orthostatic hypotension. Environmental factors such as inadequate lighting, obstacles in a walkway, loose rugs, lack of supports in a bathrooms, and slippery conditions outside are other circumstances that promote falls and fractures.

It is possible that pharmacological intervention with vitamin D would be most beneficial for patients who show signs of age-related muscle decline. This later might be demonstrated by use of grip strength [31], assessment of postural stability [32] or a timed up and go test [33]. Inability to perform this task predicts a greater likelihood of falling.

The limitations of the present study are that falls were a secondary outcome in the study, nevertheless the number of events and the long observation period compensate in part. Also this study was not designed to answer the question of fracture efficacy and much larger numbers would be needed to confirm these findings. However, the results of the studies on the vitamin D compounds suggest that this area of research might be a useful one to pursue with the goal of identifying those who might respond to this group of compounds. It is conceivable that certain vitamin D analogs could be developed that are more potent in up regulating 1,25-dihydroxyvitamin D receptors in muscle and brain and through this action be effective in reducing falls.

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