Effects of Teriparatide Compared with Risedronate on Recovery After Pertrochanteric Hip Fracture

Results of a Randomized, Active-Controlled, Double-Blind Clinical Trial at 26 Weeks

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Background: Osteoporosis drugs might affect fracture-healing. We therefore studied the effects of teriparatide in comparison with risedronate on recovery after pertrochanteric hip fractures.

Methods: The study was a randomized, multicenter, active-controlled, 78-week trial comparing teriparatide (20 μg/day) with risedronate (35 mg/week) initiated within 2 weeks after fixation of a low-trauma pertrochanteric hip fracture (AO/OTA 31-A1 or 31-A2). The main inclusion criteria were a bone mineral density T-score of ≤−2.0 and 25-OH-vitamin D of ≥9.2 ng/mL. During the first 26 weeks, patients received study medication with oral or injectable placebo plus calcium and vitamin D in a double-blinded fashion. Secondary (Timed Up-and-Go [TUG] test, hip pain, Short Form [SF]-36 health status, and safety) and exploratory (radiographic outcomes and ability to walk) 26-week end points are reported.

Results: Of the 224 patients who were randomized, 171 (86 teriparatide, 85 risedronate) were included in the analysis. The mean age was 77 ± 8 years, 77% were female, and 26% had a prior history of low-trauma fracture. The teriparatide group completed the TUG test in a shorter time at 6, 12, 18, and 26 weeks (differences of −5.7, −4.4, −3.1, and −3.1 seconds, respectively; $p = 0.021$ for the overall difference). They also reported less pain on a visual analog scale immediately after the TUG test at 12 and 18 weeks (adjusted absolute differences of 10.6 and 11.9 mm, respectively; $p < 0.05$). There were no significant between-group differences in the SF-36 score, Charnley hip pain score, ability to walk, or use of walking aids during follow-up. Radiographic healing at 6, 12, and 26 weeks, mechanical failure of the implant (teriparatide, 7; risedronate, 8), loss of reduction (teriparatide, 2; risedronate, 4), and nonunion (0 cases) were not significantly different. Mild hypercalcemia and hyperuricemia were more frequent with teriparatide.

Conclusions: Teriparatide was associated with less pain and a shorter time to complete the TUG test between 6 and 26 weeks compared with risedronate. Other fracture-recovery outcomes were similar. The results should be interpreted with caution as these were secondary end points.

Level of Evidence: Therapeutic Level II. See Instructions for Authors for a complete description of levels of evidence.

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Approximately 1 in 6 women in North America will experience a hip fracture in their lifetime[1]. Patients 55 years or older with hip fractures have an overall 1-year mortality rate of up to 39%[2], and the survivors have a decreased life expectancy, loss of physical function, and impaired quality of life[2-4], mainly because of frailty[5,6]. Hip fractures are often associated with osteoporosis, and they are strong risk factors for fractures at other skeletal sites[7,8].

The 2 major categories of pharmacological treatment for osteoporosis are antiresorptive and bone anabolic medications. Approved antiresorptives include bisphosphonates, selective estrogen receptor modulators, denosumab, and strontium ranelate.

Disclosure: The trial was funded by Eli Lilly, and two of the authors are employees of Eli Lilly. The sponsor designed the protocol with advice from external advisors and was responsible for the quality control of data collected and the statistical analysis. On the **Disclosure of Potential Conflicts of Interest** forms, *which are provided with the online version of the article,* one or more of the authors checked "yes" to indicate that the author had a relevant financial relationship in the biomedical arena outside the submitted work and "yes" to indicate that the author had other relationships or activities that could be perceived to influence, or have the potential to influence, what was written in this work.

TABLE I Summary of Key Eligibility Criteria for Trial Participants*

Inclusion criteria
Men and postmenopausal women aged ≥50 years
Ambulatory and free of severe or chronically disabling conditions, including malignant neoplasms, dementia, and gait problems (ASA score I, II, or III)
Unilateral, low-trauma fracture of the pertrochanteric region (AO/OTA types 31-A1 and 31-A2) treated with an intramedullary nail or a sliding compression hip screw
Low bone mass (BMD T-score, ≤−2 standard deviations) at the lumbar spine and/or proximal femur
Exclusion criteria
Elevated total alkaline phosphatase (>140 U/L) and/or elevated albumin-corrected serum calcium levels (≥2.65 mmol/L)
Elevated serum PTH (>72 pg/mL)
Severe serum 25-OH-vitamin D deficiency (<9.2 ng/mL)
Abnormally elevated or decreased free thyroxine levels (outside normal range of 9-24 pmol/L)
Active liver disease or clinical jaundice
Substantially impaired renal function (endogenous creatinine clearance, <30 mL/min)
Soft-tissue infection at the operative site
Treatment with bone-grafting or osteotomies
Treatment augmented using any type of degradable cement, hydroxyapatite-coated implants, or noninvasive interventions such as ultrasound, magnetic field stimulation, or electrical stimulation
Local or systemic treatment with bone morphogenetic proteins or any other growth factor
Polytrauma and fractures at multiple sites
Prior treatment with
Fluoride in therapeutic doses
Strontium ranelate for any duration
Intravenous bisphosphonates at any dose within 12 months prior to visit 1
Denosumab within 6 months prior to visit 1
PTH-(1-84), teriparatide, or other PTH analog
Contraindications to treatment with either of the 2 study drugs (teriparatide or risedronate)

*ASA = American Society of Anesthesiologists.

Teriparatide (recombinant human parathyroid hormone [PTH]-1-34) is the only currently approved anabolic medication for the treatment of osteoporosis. There is great interest in the effect of these agents on bone repair and fracture-healing in humans. To our knowledge, antiresorptive agents have not demonstrated any deleterious effects on fracture-healing[9,10], and they have shown positive effect in some animal studies[11,12]. In animal studies, teriparatide enhanced bone-healing[13-16], and post-hoc analysis of a randomized trial showed that teriparatide accelerated the time to cortical continuity of distal radial fractures at a dosage of 20 μg/day, but not at 40 μg/day[17]. A post-hoc subgroup analysis showed a positive dose-related effect on early radiographic callus formation[18]. A similar study on proximal humeral fractures failed to show any effect[19]. PTH-(1-84) seemed to improve fracture-healing in women with osteoporosis and pelvic fractures[20], although that study had important design limitations[21]. Case reports and cohort studies also suggest that teriparatide accelerates bone-healing[22].

We present the 26-week results of a randomized, double-blind trial comparing the effect of teriparatide with that of risedronate on functional and radiographic outcomes after a pertrochanteric hip fracture in men and postmenopausal women with low bone mass. The initial study design was to use physical function (the Timed Up-and-Go [TUG] test) as the primary outcome variable. However, in the final design, in order to more accurately calculate the sample size for the study, the TUG test became an important secondary end point and the primary outcome variable was the change from baseline to 18 months in bone mineral density (BMD) in the lumbar spine; these BMD results will be published elsewhere. Here we report a preplanned analysis of all secondary end points and exploratory variables related to recovery after fracture recovery and to drug safety.

Materials and Methods

From April 2009 to February 2014, hospital-based physicians from 17 countries in North America, Mexico, and Europe who were experienced in treating patients with hip fractures screened over 2,400 patients for eligibility. The majority could not enter the trial, mainly because of dementia, patient decision, or major comorbidities. A total of 389 patients with a recent pertrochanteric hip fracture were enrolled. Key eligibility criteria are summarized in Table I.

This study was a Phase-IV, randomized, multicenter, active-controlled trial with 3 periods: (1) a screening phase lasting a maximum of 14 days from surgery to randomization; (2) a double-blind, double-dummy treatment period from randomization to the 26-week visit; and (3) an open-label treatment period during which patients continued treatment up to 78 weeks with the same study drug to which they had been randomized. Here we present results from the double-blind phase of the trial.

The trial was registered at ClinicalTrials.gov (NCT00887354). It was approved by the responsible institutional review boards at each center and was conducted in accordance with the Declaration of Helsinki, good clinical practices, and applicable laws and regulations. Written informed consent was obtained from all patients before any screening procedures.

At the screening visit, all patients started oral supplements of calcium (500-1,000 mg/day) and vitamin D (800 IU/day) and discontinued any ongoing osteoporosis drug. If the baseline serum 25-OH-vitamin D level was between 9.2 and 16 ng/mL, patients received a single oral loading dose of 100,000 IU of vitamin D. At the baseline visit, patients were randomized in a 1:1 ratio to teriparatide (20 μg/day subcutaneous teriparatide injection plus weekly oral placebo) or risedronate (daily subcutaneous placebo injection plus 35 mg/week oral risedronate). Treatment assignment was stratified by the type of fracture (AO/OTA 31-A1 and 31-A2)[23] and determined by a computer-generated random sequence. All patients and investigators were blinded to the study treatments.

Secondary Outcomes (Efficacy)

Functional mobility was evaluated at the 6, 12, 18, and 26-week visits with the TUG test[24,25].

Self-reported hip pain was assessed immediately after completion of the TUG test using a linear visual analog scale (VAS) on which 0 mm represented no pain and 100 mm, the most severe pain possible[26]. In addition, a modified Charnley pain score was used to estimate the worst hip pain in the preceding 24 hours (see Appendix)[27].

Patient-rated health status was estimated with the Short Form (SF)-36 questionnaire[27-30], self-administered by the patients at the randomization visit and the 6, 12, 18, and 26-week visits. Patients also completed the questionnaire during the screening phase to assess their status during the 4 weeks before the fracture (recall SF-36 value).

The sequence for the patient-reported outcomes was (1) SF-36 survey, (2) TUG test, (3) VAS pain assessment, (4) modified Charnley hip pain score, and (5) ability to walk.

Secondary Outcomes (Safety)

Safety analyses were conducted on all patients who received ≥1 dose of medication. These included treatment-emergent adverse events (TEAEs); incident clinical fractures; analgesic use for hip pain; serum levels of 25-OH-vitamin D, calcium, and uric acid; clinical chemistry and hematology; and vital signs.

Exploratory Variables

Radiographic Outcomes

Hip radiographs were centrally adjudicated by 2 independent radiologists who were blinded to treatment assignment (Synarc). Adequate fracture reduction was defined as a femoral neck-shaft angle of 15° valgus to 10° varus relative to the contralateral, unfractured hip on an anteroposterior radiograph, posterior angulation of <20° on a lateral radiograph, and proximal fragment alignment with or superior to the distal fragment on an anteroposterior radiograph. The lag screw position was considered adequate on the basis of a tip-apex distance (TAD) of <20 mm[31] together with the criteria defined by Parker[32]. Radiographic healing was assessed by conventional anteroposterior and lateral radiographs at 6, 12, and 26 weeks. The variables for evaluating healing were predefined and included a combination of cortical bridging or softened cortical continuity, disappearance of the fracture line, stable fracture alignment compared with the preceding visit, and/or progressive sclerosis at the fracture site.

Mechanical Failure

Mechanical failure of the implant included cutting-out of the screw from the femoral head (defined as projection of the screw from the femoral head by >1 mm[32]); excessive migration of the tip of the screw within the femoral head (change in TAD of >6 mm); varus collapse with a decrease in femoral neck-shaft angle of >10°; excessive progression of offset; a sliding plate that was bent, broken, or pulled off the shaft; or loosened or broken cortical screws. Fracture nonunion was defined as the absence of radiographic healing combined with hip pain (Charnley categories 2 to 5; see Appendix) and inability to walk without assistance (nonfunctional ambulatory or nonambulatory) at 26 weeks.

Ability to Walk

Ambulatory functioning was assessed at all post-baseline visits using 4 categories: community, household, nonfunctional, and nonambulatory[33]. In addition, use of walking aids was assessed using the following categories: no aid, 1 cane, 1 crutch, 2 canes, 2 crutches, a walker, a person as support, and not walking.

Statistical Methods

Sample size estimation was based on the primary outcome of lumbar spine BMD after 18 months (results to be presented elsewhere). A difference of 0.023 g/cm^2 in BMD between the treatment groups was considered to be clinically important[34]. Assuming a common standard deviation of 0.047 g/cm^2 in each group, 76 patients per treatment arm were planned to yield 85% power at a significance level of 0.05 (2-sided test). Allowing for a 30% loss, we planned to enroll 109 patients per treatment arm. Efficacy analyses for effects on functional recovery were conducted on the full analysis set (FAS), which follows the intent-to-treat principle and includes data from all patients who received ≥1 dose of the trial drug (active or placebo) and had ≥1 follow-up visit that included any efficacy assessment.

Baseline characteristics were summarized descriptively. The analysis of the TUG test, patient-rated health status, and hip pain VAS was performed with a mixed-effects model for repeated measures (MMRM), which accounts for data missing at random by using the correlation of observations within each patient and without the need of any explicit imputations[35]. Treatment, visit, treatment-visit interaction, and type of fracture were always included as fixed effects in the MMRM. Other variables were included as prespecified, depending on the end point. TUG test results were derived from log-transformed data. All non-missing data from the FAS were analyzed. At each follow-up visit, covariate-adjusted (least squares) mean changes from baseline with standard

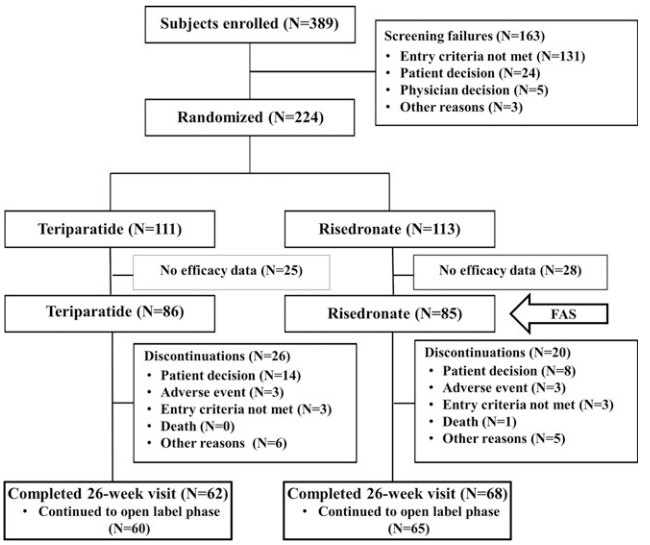

Fig. 1

Consolidated Standards of Reporting Trials (CONSORT) flow diagram showing patient disposition. The FAS includes all randomized patients who received ≥1 dose of study medication (active or placebo dummy) and had ≥1 onsite follow-up visit with any efficacy assessment. Eight randomized subjects (5 teriparatide and 3 risedronate) never took the study medication. Two enrolled subjects were not screening failures but were not randomized.

TABLE II Patient Characteristics*

	Teriparatide (N = 86)	Risedronate (N = 85)	Total (N = 171)
Age† *(yr)*	77.2 ± 8.0	76.4 ± 7.5	76.8 ± 7.7
Sex†			
Female	66 (76.7)	66 (77.6)	132 (77.2)
Male	20 (23.3)	19 (22.4)	39 (22.8)
Height† *(cm)*	163.3 ± 9.5	162.2 ± 9.5	162.8 ± 9.5
Weight† *(kg)*	66.8 ± 12.5	68.1 ± 12.0	67.1 ± 12.2
BMI† *(kg/m²)*	25.0 ± 3.9	25.8 ± 3.8	25.4 ± 3.9
History of smoking in the past 6 months†	12 (14.0)	14 (16.5)	26 (15.2)
Prior osteoporosis drug use†			
≥1 osteoporosis drug	12 (14.0)	11 (12.9)	23 (13.5)
≥1 bisphosphonate§	7 (8.1)	9 (10.6)	16 (9.4)
Other osteoporosis drugs#	6 (7.0)	3 (3.5)	9 (5.3)
Duration of prior bisphosphonate use** *(mo)*	65.6 (38.0-78.8)	24.4 (5.1-42.8)	40.4 (10.4-74.8)
Glucocorticoid use during the study†	11 (10.4)	7 (6.4)	18 (8.3)
Vitamin D megadose before randomization†,††	12 (14.0)	21 (24.7)	33 (19.3)
Dose** *(IU)*	100,000 (100,000-100,000)	100,000 (100,000-100,000)	100,000 (100,000-100,000)
Patients with ≥1 fracture between age 50 years and study entry†			
All fractures	37 (43.0)	30 (35.3)	67 (39.2)
Low-trauma fractures	27 (31.4)	17 (20.0)	44 (25.7)
No. of low-trauma fractures in such patients†	1.2 ± 0.40	1.5 ± 0.94	1.3 ± 0.67
Time from last fracture to randomization** *(yr)*			
Low-trauma fracture at any location	4.0 (0.6-10.3)	4.0 (1.6-10.5)	4.0 (1.2-10.3)
Total no. of low-trauma fractures§§,##	32	23	55
Vertebral*** *(no. [% of total])*	3 (9.4)	3 (13.0)	6 (10.9)
Nonvertebral *(no. [% of total])*	29 (90.6)	20 (87.0)	49 (89.1)
Main nonvertebral fractures††† *(no. [% of total])*	17 (53.1)	11 (47.8)	28 (50.9)
No. in safety population†††	106	110	216
Anticoagulant therapy†	96 (90.6)	102 (92.7)	198 (91.7)

*Percentages are based on the number of patients with non-missing values. Patients in the FAS are included. BMI = body mass index. †The values are given as the mean and the standard deviation. ‡The values are given as the number of patients, with the percentage in parentheses. §Alendronate, risedronate, or ibandronate. #Other osteoporosis drugs included calcium and/or vitamin D, calcitonin, selective estrogen receptor modulators, and vitamin D active metabolites. **The values are given as the median, with the interquartile range in parentheses. ††A vitamin D megadose was administered in patients with 25-OH-vitamin D levels between 9.2 and 16 ng/mL at baseline. §§A patient with fractures at multiple locations may be counted multiple times. ##Percentages are based on the total number of low-trauma fractures. ***Vertebral fractures include fractures of thoracic, lumbar, and thoracolumbar vertebrae. †††Main nonvertebral fractures include fractures of the hip, distal aspect of the femur, forearm, humerus, pelvis, ribs, and tibia. ‡‡‡The safety population includes all patients receiving ≥1 dose of study medication (active or placebo dummy).

errors were derived for the 2 treatments and p values were reported for their differences. Hip pain using the Charnley score and radiographic healing were analyzed with logistic regression with repeated measures to model the probability of a positive outcome. Frequencies of patients with surgical complications and TEAEs were compared using the Fisher exact test. All data were analyzed using SAS software (version 9.4).

Results

Patient Disposition and Baseline Characteristics

Overall, 224 patients were randomized, and 171 (86 teriparatide, 85 risedronate) contributed to the efficacy analysis. Ninety-four patients (42%) did not complete the 26-week

TABLE III Index Hip Fracture Characteristics and Surgical Details*

	Teriparatide (N = 86)	Risedronate (N = 85)	Total (N = 171)
Side†			
Right	48 (55.8)	40 (47.1)	88 (51.5)
Left	38 (44.2)	45 (52.9)	83 (48.5)
Type of fracture†‡			
AO/OTA 31-A1	38 (45.8)	45 (54.2)	83 (50.0)
AO/OTA 31-A2	45 (54.2)	37 (44.6)	82 (49.4)
Other (intracapsular)	0	1 (1.2)	1 (0.6)
Hip fracture on dominant side†	49 (57.0)	38 (44.7)	87 (50.9)
Time from hip fracture to hospital admission† *(days)*	0.5 ± 1.2	0.5 ± 1.8	0.5 (± 1.5)
Time from hip fracture to surgery§ *(days)*	2 (1-5)	2 (1-4)	2 (1-4)
Time from hip fracture to administration of first treatment dose§ *(days)*	15 (12-18)	15 (12-18)	15 (12-18)
Time from surgical repair to administration of first treatment dose§ *(days)*	9 (8-11)	10 (8-12)	9 (8-12)
Anesthesia given†			
Regional	61 (70.9)	61 (71.8)	122 (71.3)
General	25 (29.1)	24 (28.2)	49 (28.7)
Reduction†			
Closed	77 (89.5)	71 (83.5)	148 (86.5)
Open	9 (10.5)	14 (16.5)	23 (13.5)
Duration of surgery from incision to closure§ *(min)*	60 (40-70)	60 (40-87)	60 (40-80)
Reaming of the diaphysis†			
Yes	19 (22.1)	8 (9.5)	27 (15.9)
No	67 (77.9)	76 (90.5)	143 (84.1)
Patients needing ≥1 blood transfusion†	13 (15.1)	20 (23.5)	33 (19.3)
Type of trochanteric implant used†			
Trochanteric intramedullary nail	53 (61.6)	44 (51.8)	97 (56.7)
Sliding hip screw system	33 (38.4)	41 (48.2)	74 (43.3)
Duration of hospital stay§ *(days)*	12 (9-15)	11 (8-15)	12 (9-15)
Discharge destination†			
Rehabilitation hospital	46 (53.5)	39 (45.9)	85 (49.7)
Home	37 (43.0)	44 (51.8)	81 (47.4)
Nursing home	3 (3.5)	2 (2.4)	Five (2.9)
Overall adequate reduction†‡#			
Yes	63 (94)	62 (93.9)	125 (94.0)
No	4 (6.0)	4 (6.1)	8 (6.0)
Missing	19 (22.1)	19 (22.4)	38 (22.2)
Adequate position of the lag screw†‡**			
Yes	77 (97.5)	75 (96.2)	152 (96.8)
No	2 (2.5)	3 (3.8)	Five (3.2)
Missing	7 (8.1)	7 (8.2)	14 (8.2)
Lag screw position‡			
TAD§ *(mm)*	17.8 (12.2-22.8)	16.4 (12.2-21.3)	17.2 (12.2-21.6)
TAD ≤20 mm†	52 (65.8)	54 (71.1)	106 (68.4)
Missing†	7 (8.1)	9 (10.6)	16 (9.4)

*Percentages are based on the number of patients with non-missing values. Patients in the FAS are included. †The values are given as the number of patients, with the percentage in parentheses. ‡As determined by the independent radiologists. The values are given as the mean and the standard deviation. §The values are given as the median, with the interquartile range in parentheses. #Criteria for adequate reduction: femoral-neck angle, anatomical to 15° valgus or 10° varus on anteroposterior radiograph; posterior angulation: <20° on lateral radiograph; proximal fragment: not inferior to the distal fragment on the anteroposterior radiograph. **An adequate position of the lag screw is achieved when the tip of the screw is placed central and central, inferior and central, or inferior and posterior within the femoral head.

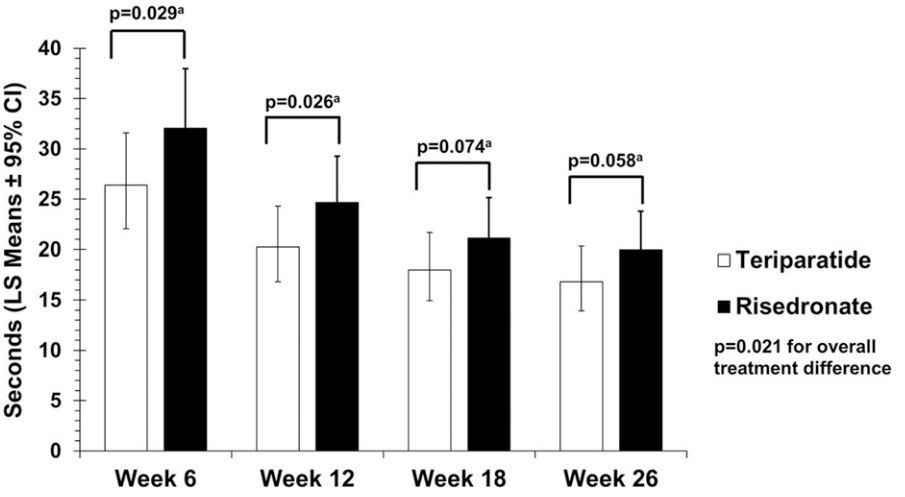

Fig. 2

Assessment of functional mobility by the time to complete the TUG test. Age, visit, type of walking aid, SF-36 physical component summary at the screening visit, and a satisfactory Charnley hip pain score at baseline were significantly associated with the outcome. [a]MMRM analysis (with log-transformation); variables in the full model included treatment, visit, treatment-visit interaction, age, type of fracture, type of reduction, type of walking aid, recall SF-36 physical component score, and baseline Charnley hip pain score. The total number of patients who contributed to the MMRM was 157 (79 teriparatide, 78 risedronate). CI = confidence interval, and LS = least squares.

visit (Fig. 1). Patient characteristics and characteristics of the index hip fracture and surgery are summarized in Tables II and III. Details regarding the implants are reported in the Appendix.

Secondary Outcomes

Functional Mobility

Overall, the time required to complete the TUG test was shorter with teriparatide than with risedronate at 6, 12, 18, and 26 weeks (differences of −5.7, −4.4, −3.1, and −3.1 seconds, respectively; p = 0.021 for the overall between-treatment difference). The least-squares mean times with teriparatide and risedronate were 26.4 and 32.1 seconds (p = 0.029) at 6 weeks, 20.2 and 24.7 seconds (p = 0.026) at 12 weeks, 18.0 and 21.2 seconds (p = 0.074) at 18 weeks, and 16.8 and 20.0 seconds (p = 0.058) at 26 weeks, respectively (Fig. 2; see Appendix). Post-hoc analysis of unadjusted data showed similar results (data not shown).

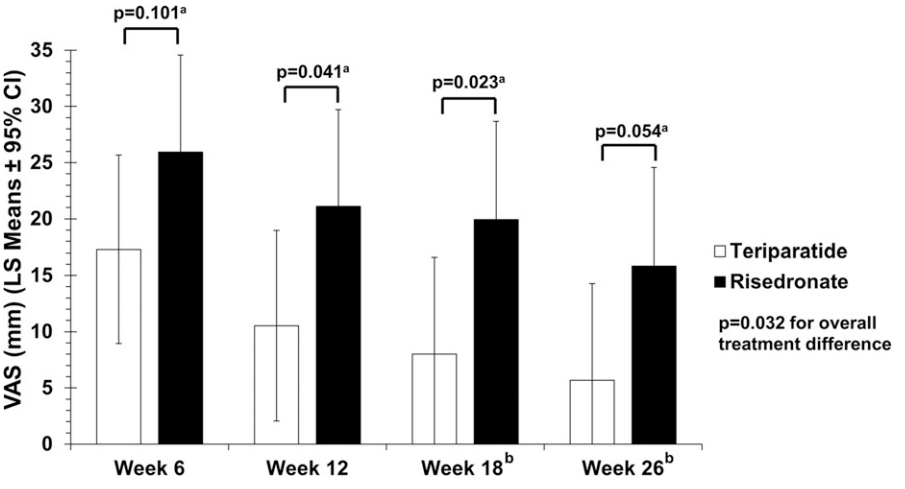

Fig. 3

Evaluation of self-reported hip pain during the TUG test using a 100-mm VAS. Visit, adequate reduction, and the interaction between treatment and adequate reduction were significantly associated with the outcome. [a]MMRM analysis; variables in the full model included treatment, visit, treatment-visit interaction, type of fracture, type of reduction, adequacy of reduction, use of opioids, and use of nonsteroidal anti-inflammatory drugs. [b]The lower confidence interval crosses zero for teriparatide. The total number of patients who contributed to the MMRM was 126 (63 in each treatment arm). LS = least squares.

TABLE IV Patient-Rated Health Status by SF-36 Questionnaire Physical Function Component*

	Teriparatide (N = 67)	Risedronate (N = 66)	P Value†
Visit 1 (recall SF-36)‡	45.7 (13.4)	47.3 (12.0)	
Visit 2 (baseline)§#	30.1 (1.51)	31.8 (1.53)	
Week 6#	37.6 (1.52)	36.8 (1.52)	0.205
Week 12#	41.5 (1.55)	42.6 (1.53)	0.737
Week 18#	44.5 (1.57)	44.6 (1.55)	0.435
Week 26#	46.4 (1.59)	45.8 (1.55)	0.267

*P < 0.001 versus baseline for both drugs at 6, 12, 18, and 26 weeks. †Using MMRM; full model adjusted by treatment, visit, treatment-visit interaction, sex, age, adequacy of reduction, and type of fracture (AO/OTA 31-A1 vs. 31-A2). ‡The values are given as the mean and the standard deviation. §Randomization visit. #The values are given as the least-squares mean and the standard error.

Self-Reported Hip Pain

VAS-assessed hip pain during the TUG test was reduced with teriparatide compared with risedronate (p = 0.032 for the between-treatment difference). The adjusted absolute difference was 10.6 mm at 12 weeks (p = 0.041), 11.9 mm at 18 weeks (p = 0.023), and 10.1 mm at 26 weeks (p = 0.054) (Fig. 3; see Appendix). Logistic regression analysis found no significant difference in the number of patients experiencing a satisfactory Charnley hip pain score between treatment arms at any time point (see Appendix).

TABLE V Safety Analyses*

	Teriparatide (N = 106)	Risedronate (N = 110)	Total (N = 216)	Fisher P Value
Adverse events†				
Any TEAE	52 (49.1)	50 (45.5)	102 (47.2)	0.683
Leading to discontinuation	5 (4.7)	6 (5.5)	11 (5.1)	1.000
Serious TEAE	14 (13.2)	21 (19.1)	35 (16.2)	0.271
Leading to hospitalization	12 (11.3)	15 (13.6)	27 (12.5)	0.683
Death	2 (1.9)	5 (4.5)	7 (3.2)	0.446
Clinical fractures				
Patients with ≥1 clinical fracture†	3 (2.8)	7 (6.4)	10 (4.6)	0.333
No. of new fractures	3	8	11	0.140‡
Hip	2	5	7	
Humerus	1	1	2	
Pelvis	0	2	2	
Clinical vertebral	0	0	0	
Laboratory parameters				
Serum 25-OH-vitamin D at 26 wk§ *(pmol/mL)*	62.2 ± 16.4 [n = 62]	71.3 ± 20.3 [n = 66]		0.006
Serum alkaline phosphatase at 26 wk§ *(IU/L)*	95.7 ± 29.3 [n = 62]	83.6 ± 21.9 [n = 64]		0.010
Serum cholesterol at 26 wk§ *(mmol/L)*	4.96 ± 1.11 [n = 85]	5.31 ± 1.08 [n = 83]		0.044#
Hypercalcemia†,**				
6 wk	7 (7.4) [n = 81]	5 (5.1) [n = 78]		0.766
26 wk	8 (12.9) [n = 62]	1 (1.5) [n = 62]		0.032
Hyperuricemia†,††				
6 wk	13 (15.9) [n = 82]	4 (5.1) [n = 79]		0.038
26 wk	9 (14.5) [n = 62]	6 (9.4) [n = 64]		0.420

*Safety analyses included all patients receiving ≥1 dose of study medication (active or placebo dummy). Percentages are based on the number of patients with non-missing values. †The values are given as the number of patients, with the percentage in parentheses and with or without the number of patients with data in brackets. ‡Poisson regression. §The values are given as the mean and the standard deviation, with or without the number of patients with data in brackets. #Last observation carried forward analysis. **Albumin-corrected serum calcium, >10.6 mg/dL. ††Serum uric acid, >8.3 mg/dL in men and >7.5 mg/dL in women.

Patient-Rated Health Status

There was no significant between-treatment difference in the change from baseline for any of the 8 domains of the SF-36 at any time point (Table IV). Depending on the domain, values returned to the pre-fracture status by 12 to 18 weeks. Age and sex were associated with the physical function domain results. In contrast, the type of fracture and adequacy of the reduction were not associated with any of the domain results (data not shown).

Safety

Treatment compliance (defined as not having missed >25% of the study medication at 2 consecutive visits) was 98.6% for teriparatide and 100% for risedronate. This information was not fully available in 37 patients. Fewer patients receiving teriparatide than risedronate died or reported serious TEAEs or clinical fractures, but the differences were not significant (Table V). There were 3 new fractures in the teriparatide group and 8 in the risedronate group ($p = 0.14$); no clinical vertebral fractures were diagnosed. At 26 weeks, the overall rate of analgesic use was 21% and was similar in both treatment arms ($p = 0.85$). Hyperuricemia and hypercalcemia were more frequent with teriparatide at the 6 and 26-week follow-up visits, respectively (Table V). Serum alkaline phosphatase was higher ($p = 0.01$) and serum cholesterol was lower ($p = 0.04$) with teriparatide (Table V). Other laboratory parameters and vital signs were not significantly different between the 2 treatment arms.

Exploratory Variables

Radiographic Outcomes

At 26 weeks, 100% of the 62 patients with data who received teriparatide and 98% of the 64 with data who received risedronate had achieved radiographic healing. By 12 weeks, the rate had been 89% to 90% in both groups. There were no significant differences in the frequency of implant failure or

TABLE VI Radiographic Findings

Radiographic Outcome	Teriparatide*	Risedronate*	Total*	Fisher P Value
Fracture-healing				
Evidence of radiographic healing†				
Week 6	n = 81	n = 81	n = 162	
Present	0	0	0	ND‡
Week 12	n = 69	n = 74	n = 143	
Present	62 (89.9)	66 (89.2)	128 (89.5)	1.000
Week 26	n = 62	n = 64	n = 126	
Present	62 (100)	63 (98.4)	125 (99.2)	1.000
Time to radiographic healing§ *(days)*	86 (84-91)	84 (84-87)		0.547#
Fracture nonunion**	0 (0)	0 (0)		ND‡
Mechanical failure of implant	n = 62	n = 64	n = 126	
Patients with >1 mechanical failure	7 (11.3)	8 (12.5)	15 (11.9)	0.577
Reason for implant failure				
Varus collapse††	0	1 (1.6)	1 (0.8)	
Side plate bent, broken, or pulled off	1 (1.6)	1 (1.6)	2 (1.6)	
Loosening of cortical screws	1 (1.6)	0	1 (0.8)	
Excessive progression of offset‡‡	5 (8.1)	7 (10.9)	12 (9.5)	
Implant cut-out	1 (1.6)	1 (1.6)	2 (1.6)	
Loss of reduction§§	n = 63	n = 62	n = 125	
Present	2 (3.2)	4 (6.5)	6 (4.8)	0.440
Absent	61 (96.8)	58 (93.5)	119 (95.2)	
Missing	23 (36.5)	23 (37.1)	46 (36.8)	

*The values are given as the number of patients, with the percentage in parentheses, except where otherwise noted. Percentages are based on the number of patients with non-missing values. †Radiographic criteria for fracture-healing: an invisible or sclerotic fracture line, cortical bridging or softened cortical continuity, and stable fracture alignment compared with preceding visit. ‡ND = not determined. §The values are given as the median, with the interquartile range in parentheses. #Log-rank test. **Nonunion was defined as the absence of radiographic healing associated with hip pain (i.e., Charnley hip pain score of ≥3) and the inability to walk without assistance at 26 weeks after randomization. ††Femoral neck-shaft angle >10°. ‡‡Excessive progression of offset was defined as >20% offset deviation of the operatively treated hip compared with the contralateral hip. Offset could not be calculated in 18 patients because of the lack of contralateral hip radiographs. §§Loss of reduction was defined as a change from "No" at Week 6 to "Yes" in any of these variables at any later visit: (a) femoral-neck angle, anatomical to 15° valgus or 10° varus on the anteroposterior radiograph; (b) posterior angulation, <20° on the lateral radiograph; and (c) proximal fragment alignment with or superior to the distal fragment on the anteroposterior radiograph.

loss of reduction between the 2 treatment arms (Table VI). No patient showed fracture nonunion (Table VI).

Ability to Walk

There were no significant differences between treatment groups at any follow-up period with respect to the ability to walk or the use of walking aids. By 26 weeks, all patients were ambulatory except for 1 in the teriparatide arm. No walking aid was needed by 36 patients (58%) receiving teriparatide and 36 (55%) receiving risedronate ($p = 0.8$).

Discussion

The overall trial was designed to evaluate a primary variable not related to recovery from fracture. However, judging by secondary outcomes (TUG test and pain during the test), teriparatide appears to be associated with a better early functional outcome after pertrochanteric hip fractures compared with risedronate. This earlier recovery of function might possibly reflect an earlier mature fracture union due to teriparatide, even though the study was not designed to show that per se. The alternative that teriparatide had other non-fracture-related effects appears unlikely, lacking biological plausibility. A third possibility would be that risedronate had a negative effect, which appears unlikely, as bisphosphonates have been shown not to impair healing in comparison with placebo[36-38], with the potential exception of distal radial fractures[39], and likely improve implant fixation[40]. A positive effect of teriparatide on human fracture recovery would not be surprising, considering the positive effect on bone-healing in various animal models[13-16,21,41].

Other secondary efficacy outcomes (SF-36, Charnley score, and ability to walk) showed no significant differences. However, the TUG test might be considered more clinically relevant than the SF-36 in these patients, as it better predicts future walking activity and activity level[25], and a rapid return to function is likely to diminish the rate of late complications and falls[24,42]. Moreover, patient-reported health-related quality of life is a consequence of both hip function and other unrelated factors, which add sources of variation. We therefore consider the TUG test not only more important, but also more sensitive, than the other secondary outcome variables. The absolute differences in the time to complete the TUG test between the 2 treatments were larger than the 1.4 to 2.4 seconds considered to be the minimal clinically important difference for this test[43,44]. Still, these results are only hypothesis-generating.

The absence of significant differences in radiographic healing is notable. However, the radiographic variables were coarse and appeared to miss the relevant time points, as no fractures were radiographically "healed" at the first examination (at 6 weeks) and the vast majority were at the second time point (at 12 weeks). Moreover, development of callus or disappearance of the fracture line is unreliable for assessing clinical healing of hip fractures[45,46]. Given the small number of radiographs that can be made to monitor fracture-healing—especially in frail subjects with hip fractures—this end point was exploratory, and not among the predetermined secondary outcomes.

To our knowledge, there is no trial that has unequivocally demonstrated improved fracture-healing with teriparatide in humans to date. A proof-of-concept, placebo-controlled trial has shown accelerated healing of wrist fractures, but the primary outcome of that study, using the higher teriparatide dose, was not significant[17,18]. A similar trial on proximal humeral fractures could not show any effect[19]. A trial on pelvic fractures in women with osteoporosis treated using human PTH-(1-84) showed an extraordinary acceleration of healing[20]. However, there is a risk of bias in that study, as the investigator was aware of the planned treatment when deciding whether or not to include a patient. Moreover, the TUG test time appeared to be remarkably long in that investigation[21]. A retrospective study of unstable pertrochanteric fractures suggested a reduction of approximately 3 weeks in the time to radiographic union with teriparatide compared with unblinded controls[47]. Apart from these studies, there are only case series available, which often suggest a beneficial effect of osteoporosis treatment on fracture-healing. The adjustment for confounders in those studies was often insufficient because of limited data or sample size[21,48].

To our knowledge, this study is the first prospective, randomized, blinded study to analyze osteoporosis drug effects on functional recovery after a hip fracture, which is a difficult clinical model to assess[49]. Methodological strengths are the predefined analysis plan, using validated instruments to measure functional outcomes and pain, and the central, blinded reading of the radiographs using prespecified diagnostic criteria. Biases were avoided through a double-dummy design and complete blinding. We allowed patients who were already using osteoporosis drugs to participate.

Limitations include the fact that the study was primarily designed to measure the effects on spinal BMD and that fracture recovery was a secondary outcome. Thus, all variables either were testing secondary hypotheses or were exploratory. We had not formally ranked the SF-36, TUG test, and pain for importance, so our emphasis on the TUG test might have been biased by the outcome. The strict eligibility criteria for the trial were aimed at reducing the variability in the patient cohort, but it created a selection bias toward a healthier population and thus limited external validity for more impaired subjects with comorbidities such as dementia or a history of malignancy. Finally, we had a very high dropout rate and low compliance with visits and study procedures. This is not unexpected in frail, elderly subjects with a severe fracture, and it stresses the difficulties of performing randomized clinical trials involving frequent, cumbersome postoperative assessments in elderly patients with fractures in whom transportation issues are substantial.

In conclusion, the improved functional performance and reduced hip pain with teriparatide concur with previous studies suggesting, but not unequivocally showing, that teriparatide may improve acute fracture-healing.

Appendix

eA Tables showing the modified Charnley pain score and measured pain categories, details of the surgical implants,

and measured TUG test times and hip pain levels are available with the online version of this article as a data supplement at jbjs.org. ■

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References

1. Cummings SR, Black DM, Rubin SM. Lifetime risks of hip, Colles', or vertebral fracture and coronary heart disease among white postmenopausal women. Arch Intern Med. 1989 Nov;149(11):2445-8.
2. Koot VC, Peeters PH, de Jong JR, Clevers GJ, van der Werken C. Functional results after treatment of hip fracture: a multicentre, prospective study in 215 patients. Eur J Surg. 2000 Jun;166(6):480-5.
3. Vidán M, Serra JA, Moreno C, Riquelme G, Ortiz J. Efficacy of a comprehensive geriatric intervention in older patients hospitalized for hip fracture: a randomized, controlled trial. J Am Geriatr Soc. 2005 Sep;53(9):1476-82.
4. Boonen S, Autier P, Barette M, Vanderschueren D, Lips P, Haentjens P. Functional outcome and quality of life following hip fracture in elderly women: a prospective controlled study. Osteoporos Int. 2004 Feb;15(2):87-94. Epub 2003 Nov 7.
5. Michaëlsson K, Nordström P, Nordström A, Garmo H, Byberg L, Pedersen NL, Melhus H. Impact of hip fracture on mortality: a cohort study in hip fracture discordant identical twins. J Bone Miner Res. 2014 Feb;29(2):424-31.
6. Cameron ID, Chen JS, March LM, Simpson JM, Cumming RG, Seibel MJ, Sambrook PN. Hip fracture causes excess mortality owing to cardiovascular and infectious disease in institutionalized older people: a prospective 5-year study. J Bone Miner Res. 2010 Apr;25(4):866-72.
7. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA. 2009 Feb 4;301(5):513-21.
8. van Staa TP, Leufkens HG, Cooper C. Does a fracture at one site predict later fractures at other sites? A British cohort study. Osteoporos Int. 2002 Aug;13(8):624-9.
9. Adami S, Libanati C, Boonen S, Cummings SR, Ho PR, Wang A, Siris E, Lane J, Adachi JD, Bhandari M, de Gregorio L, Gilchrist N, Lyritis G, Möller G, Palacios S, Pavelka K, Heinrich R, Roux C, Uebelhart D; FREEDOM Fracture-Healing Writing Group. Denosumab treatment in postmenopausal women with osteoporosis does not interfere with fracture-healing: results from the FREEDOM trial. J Bone Joint Surg Am. 2012 Dec 5;94(23):2113-9.
10. Larsson S, Fazzalari NL. Anti-osteoporosis therapy and fracture healing. Arch Orthop Trauma Surg. 2014 Feb;134(2):291-7. Epub 2012 Jun 9.
11. Aspenberg P. Drugs and fracture repair. Acta Orthop. 2005 Dec;76(6):741-8.
12. Little DG, McDonald M, Bransford R, Godfrey CB, Amanat N. Manipulation of the anabolic and catabolic responses with OP-1 and zoledronic acid in a rat critical defect model. J Bone Miner Res. 2005 Nov;20(11):2044-52. Epub 2005 Jul 18.
13. Andreassen TT, Ejersted C, Oxlund H. Intermittent parathyroid hormone (1-34) treatment increases callus formation and mechanical strength of healing rat fractures. J Bone Miner Res. 1999 Jun;14(6):960-8.

14. Alkhiary YM, Gerstenfeld LC, Krall E, Westmore M, Sato M, Mitlak BH, Einhorn TA. Enhancement of experimental fracture-healing by systemic administration of recombinant human parathyroid hormone (PTH 1-34). J Bone Joint Surg Am. 2005 Apr;87(4):731-41.

15. Barnes GL, Kakar S, Vora S, Morgan EF, Gerstenfeld LC, Einhorn TA. Stimulation of fracture-healing with systemic intermittent parathyroid hormone treatment. J Bone Joint Surg Am. 2008 Feb;90(Suppl 1):120-7.

16. Komrakova M, Stuermer EK, Werner C, Wicke M, Kolios L, Sehmisch S, Tezval M, Daub F, Martens T, Witzenhausen P, Dullin C, Stuermer KM. Effect of human parathyroid hormone hPTH (1-34) applied at different regimes on fracture healing and muscle in ovariectomized and healthy rats. Bone. 2010 Sep;47(3):480-92. Epub 2010 May 16.

17. Aspenberg P, Genant HK, Johansson T, Nino AJ, See K, Krohn K, García-Hernández PA, Recknor CP, Einhorn TA, Dalsky GP, Mitlak BH, Fierlinger A, Lakshmanan MC. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. J Bone Miner Res. 2010 Feb;25(2):404-14.

18. Aspenberg P, Johansson T. Teriparatide improves early callus formation in distal radial fractures. Acta Orthop. 2010 Apr;81(2):234-6.

19. Johansson T. PTH 1-34 (teriparatide) may not improve healing in proximal humerus fractures. A randomized, controlled study of 40 patients. Acta Orthop. 2016 Feb;87(1):79-82. Epub 2015 Jul 15.

20. Peichl P, Holzer LA, Maier R, Holzer G. Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. J Bone Joint Surg Am. 2011 Sep 7;93(17):1583-7.

21. Aspenberg P. Annotation: parathyroid hormone and fracture healing. Acta Orthop. 2013 Feb;84(1):4-6. Epub 2013 Jan 31.

22. Zhang D, Potty A, Vyas P, Lane J. The role of recombinant PTH in human fracture healing: a systematic review. J Orthop Trauma. 2014 Jan;28(1):57-62.

23. Marsh JL, Slongo TF, Agel J, Broderick JS, Creevey W, DeCoster TA, Prokuski L, Sirkin MS, Ziran B, Henley B, Audigé L. Fracture and dislocation classification compendium - 2007: Orthopaedic Trauma Association classification, database and outcomes committee. J Orthop Trauma. 2007 Nov-Dec;21(10) (Suppl):S1-133.

24. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991 Feb;39(2):142-8.

25. Ingemarsson AH, Frändin K, Mellström D, Möller M. Walking ability and activity level after hip fracture in the elderly—a follow-up. J Rehabil Med. 2003 Mar;35 (2):76-83.

26. Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. Pain. 1983 May;16(1):87-101.

27. Tidermark J, Bergström G, Svensson O, Törnkvist H, Ponzer S. Responsiveness of the EuroQol (EQ 5-D) and the SF-36 in elderly patients with displaced femoral neck fractures. Qual Life Res. 2003 Dec;12(8):1069-79.

28. Jaglal S, Lakhani Z, Schatzker J. Reliability, validity, and responsiveness of the lower extremity measure for patients with a hip fracture. J Bone Joint Surg Am. 2000 Jul;82(7):955-62.

29. Peterson MG, Allegrante JP, Cornell CN, MacKenzie CR, Robbins L, Horton R, Ganz SB, Augurt A. Measuring recovery after a hip fracture using the SF-36 and Cummings scales. Osteoporos Int. 2002;13(4):296-302.

30. Mattsson P, Alberts A, Dahlberg G, Sohlman M, Hyldahl HC, Larsson S. Resorbable cement for the augmentation of internally-fixed unstable trochanteric fractures. A prospective, randomised multicentre study. J Bone Joint Surg Br. 2005 Sep;87(9):1203-9.

31. Baumgaertner MR, Solberg BD. Awareness of tip-apex distance reduces failure of fixation of trochanteric fractures of the hip. J Bone Joint Surg Br. 1997 Nov;79 (6):969-71.

32. Parker MJ. Cutting-out of the dynamic hip screw related to its position. J Bone Joint Surg Br. 1992 Jul;74(4):625.

33. Koval KJ, Aharonoff GB, Su ET, Zuckerman JD. Effect of acute inpatient rehabilitation on outcome after fracture of the femoral neck or intertrochanteric fracture. J Bone Joint Surg Am. 1998 Mar;80(3):357-64.

34. Leslie WD, Majumdar SR, Morin SN, Lix LM. Change in bone mineral density is an indicator of treatment-related antifracture effect in routine clinical practice: a registry-based cohort study. Ann Inter Med. 2016 Jul 19. [Epub ahead of print].

35. Mallinckrodt CH, Clark WS, David SR. Accounting for dropout bias using mixed-effects models. J Biopharm Stat. 2001 Feb-May;11(1-2):9-21.

36. Colón-Emeric C, Nordsletten L, Olson S, Major N, Boonen S, Haentjens P, Mesenbrink P, Magaziner J, Adachi J, Lyles KW, Hyldstrup L, Bucci-Rechtweg C, Recknor C; HORIZON Recurrent Fracture Trial. Association between timing of zoledronic acid infusion and hip fracture healing. Osteoporos Int. 2011 Aug;22 (8):2329-36. Epub 2010 Dec 9.

37. Kim TY, Ha YC, Kang BJ, Lee YK, Koo KH. Does early administration of bisphosphonate affect fracture healing in patients with intertrochanteric fractures? J Bone Joint Surg Br. 2012 Jul;94(7):956-60.

38. Xue D, Li F, Chen G, Yan S, Pan Z. Do bisphosphonates affect bone healing? A meta-analysis of randomized controlled trials. J Orthop Surg Res. 2014;9:45. Epub 2014 Jun 5.

39. Molvik H, Khan W. Bisphosphonates and their influence on fracture healing: a systematic review. Osteoporos Int. 2015 Apr;26(4):1251-60. Epub 2015 Jan 9.

40. Hilding M, Aspenberg P. Local peroperative treatment with a bisphosphonate improves the fixation of total knee prostheses: a randomized, double-blind radiostereometric study of 50 patients. Acta Orthop. 2007 Dec;78(6):795-9.

41. Grosso MJ, Courtland HW, Yang X, Sutherland JP, Stoner K, Nguyen J, Fahlgren A, Ross FP, van der Meulen MC, Bostrom MP. Intermittent PTH administration and mechanical loading are anabolic for periprosthetic cancellous bone. J Orthop Res. 2015 Feb;33(2):163-73. Epub 2014 Nov 18.

42. Okumiya K, Matsubayashi K, Nakamura T, Fujisawa M, Osaki Y, Doi Y, Ozawa T. The timed "up & go" test is a useful predictor of falls in community-dwelling older people. J Am Geriatr Soc. 1998 Jul;46(7):928-30.

43. Wright AA, Cook CE, Baxter GD, Dockerty JD, Abbott JH. A comparison of 3 methodological approaches to defining major clinically important improvement of 4 performance measures in patients with hip osteoarthritis. J Orthop Sports Phys Ther. 2011 May;41(5):319-27. Epub 2011 Feb 18.

44. Kristensen MT, Henriksen S, Stie SB, Bandholm T. Relative and absolute intertester reliability of the timed up and go test to quantify functional mobility in patients with hip fracture. J Am Geriatr Soc. 2011 Mar;59(3):565-7.

45. Szechinski JW, Grigorian MA, Grainger AJ, Elliott JM, Wischer TK, Peterfy CG, Genant HK. Femoral neck and intertrochanteric fractures: radiographic indicators of fracture healing. Orthopedics. 2002 Dec;25(12):1365-8; discussion 1368.

46. Morshed S, Bhandari M. Clinical trial design in fracture-healing research: meeting the challenge. J Bone Joint Surg Am. 2008 Feb;90(Suppl 1):55-61.

47. Huang TW, Yang TY, Huang KC, Peng KT, Lee MS, Hsu RW. Effects of teriparatide on unstable pertrochanteric fractures. BioMed Res Int. 2015;2015:568390.

48. Campbell EJ, Campbell GM, Hanley DA. The effect of parathyroid hormone and teriparatide on fracture healing. Expert Opin Biol Ther. 2015 Jan;15(1):119-29. Epub 2014 Nov 3.

49. Kanakaris NK, West RM, Giannoudis PV. Enhancement of hip fracture healing in the elderly: evidence deriving from a pilot randomized trial. Injury. 2015 Aug;46 (8):1425-8.