Incidence of hip and subtrochanteric/femoral shaft fractures in postmenopausal women with osteoporosis in the phase 3 long-term odanacatib fracture trial

Papapoulos, Socrates, Bone, Henry, Cosman, Felicia, Dempster, David W., McClung, Michael R., Nakamura, Toshitaka, Restrepo, José Fernando Molina, Bouxsein, Mary L., Cohn, Dosinda, de Papp, Anne, Massaad, Rachid and Santora, Arthur

Papapoulos Socrates (Orcid ID: 0000-0003-2243-6940)

Cosman Felicia (Orcid ID: 0000-0003-4554-6616)

Dempster David (Orcid ID: 0000-0002-2262-4039)

McClung Michael (Orcid ID: 0000-0002-7827-0778)

Bouxsein Mary (Orcid ID: 0000-0002-7027-7414)

Incidence of Hip and Subtrochanteric/Femoral Shaft Fractures in Postmenopausal Women with Osteoporosis in the Phase 3 Long-Term Odanacatib Fracture Trial

Socrates Papapoulos, MD,[1] Henry Bone, MD,[2] Felicia Cosman, MD,[3] David W. Dempster, PhD,[3] Michael R. McClung, MD,[4] Toshitaka Nakamura, MD,[5] José Fernando Molina Restrepo, MD,[6] Mary L. Bouxsein, PhD,[7] Dosinda Cohn MS,[8] Anne de Papp, MD,[8] Rachid Massaad, PhD,[9] and Arthur Santora, MD[8]

[1]Leiden University Medical Center, Leiden, The Netherlands

[2]Michigan Bone & Mineral Clinic, Detroit, MI, USA

[3]Columbia University, New York, NY, USA

[4]Oregon Osteoporosis Center, Portland, OR, USA, and Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia

[5]University of Occupational and Environmental Health, Fukuoka, Japan

[6]Reumalab, Medellín, Colombia

[7]Center for Advanced Orthopedic Studies, Beth Israel Deaconess Medical Center, and Department of Orthopedic Surgery, Harvard Medical School, Boston, MA, USA

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jbmr.4284

[8]Merck & Co., Inc., Kenilworth, NJ, USA

[9]MSD Europe Inc., Brussels, Belgium

Address correspondence to: Socrates Papapoulos, Center for Bone Quality, Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, The Netherlands.

E-mail: S.E.Papapoulos@lumc.nl; Tel: +31 71 526 2490; ORCID: 0000-0003-2243-6940

Running title: Femur fractures in LOFT

Supplemental File 1. Fracture trial protocol (protocol number 018)

Supplemental File 2. Pharmacogenetics

Supplemental File 3. Individual case descriptions of patients with AFF

ABSTRACT (290/300 words)

We prospectively assessed, with predefined criteria, the location and rates of all femur fractures (hip, subtrochanteric/femoral shaft [ST/FS], including atypical [AFF], and distal fractures) in women at increased fracture risk during treatment with the cathepsin K inhibitor, odanacatib (ODN), or placebo over 5 years in the Long-Term ODN Fracture Trial (LOFT and LOFT Extension [NCT00529373, EudraCT 2007-002693-66]). ODN was an investigational antiresorptive agent previously in development as an osteoporosis treatment that, unlike bisphosphonates, reduces bone formation only transiently. Women aged ≥65 years with a BMD T-score ≤-2.5 at the TH or FN, or with a radiographic vertebral fracture and T-scores ≤-1.5 at the TH or FN, were randomized (1:1) to receive ODN 50 mg/week or placebo. All patients received vitamin D_3 (5600 IU/week) and calcium (total 1200 mg/day); the analysis included 16,071 women. Rates of all adjudicated low-energy femoral fractures were 0.38 versus 0.58/100 patient-years for ODN and placebo, respectively (hazard ratio [HR] 0.65; 95% CI 0.51, 0.82; nominal $p<0.001$), and for low-energy hip fractures were 0.29 versus 0.56/100 patient-years, respectively (HR 0.52; 95% CI 0.40, 0.67; $p<0.001$). The cumulative incidence of combined hip and ST/FS or hip fractures alone in the ODN group was consistently lower than in the placebo group (1.93% versus 3.11% for combined fractures, and 1.53% versus 3.03% for hip fractures at 5 years, respectively). However, low-energy ST/FS fractures were more frequent in ODN-treated women than placebo-treated women (24 versus 6, respectively). Among these, 12 fractures were adjudicated as AFF in 10 patients treated with ODN (0.03/100 patient-years); compared with none in the six placebo-treated women (estimated difference, 0.03 (95% CI 0.02, 0.06). These results provide insight into possible pathogeneses of AFF, suggesting that the current criteria for diagnosing these fractures may need to be reconsidered.

KEY WORDS (from journal-defined list)**:** Biochemical markers of bone turnover, clinical trials, osteoporosis, therapeutics

Introduction

Fractures of the subtrochanteric region and the diaphysis of the femur (subtrochanteric/femoral shaft [ST/FS] fractures) represent about 5–10% of all fractures of the femur in epidemiological studies (reviewed by Shane et al).[1,2] After the age of 60 years, these fractures are more common in women than in men; their reported incidence increases steeply with age, parallel to that of hip fractures, and they occur mainly after low-energy trauma, similar to other osteoporotic fractures.[1,3] Radiographically, such fractures are mainly spiral or oblique in appearance, but transverse fractures have also been reported.[4] In recent years, ST/FS fractures, with clinical and radiographic features thought to be unusual for osteoporosis, attracted the attention of physicians, regulatory authorities, the public, and the media because of their reported association with the use of bisphosphonates. The incidence, risk factors, and pathogenesis of these fractures, termed atypical femoral fractures (AFFs), have been reviewed by a Task Force of the ASBMR and a Working Group of the International Osteoporosis Foundation and the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and criteria for their diagnosis were proposed.[1,2,5] An updated extensive review of the epidemiology and management of AFFs and their relationship with bisphosphonate treatment was recently published.[6] The main findings of this review was that although they have been reported in treatment-naïve patients, AFFs are more frequent in patients on bisphosphonate therapy and that long-term use of bisphosphonates may be associated with a higher risk for these fractures. However, the absolute risk of AFF in bisphosphonate-treated patients is very low.

The frequency and characteristics of ST/FS and AFFs have been investigated by two types of studies: studies of large databases that used International Classification of Disease

(ICD) codes to identify ST/FS fractures with no radiographic review; and retrospective cohort studies with radiographic adjudication of identified cases. There are no prospective studies of the incidence of ST/FS in patients with osteoporosis treated with bisphosphonates. Post-hoc analyses of the results of clinical trials with alendronate, zoledronate, and risedronate reported a low incidence of ST/FS fractures that was not different between placebo- and bisphosphonate-treated patients, but the original radiographs were not available to adjudicate AFFs.[7,8] AFFs were, however, prospectively assessed in the ARCH study in which women with osteoporosis received blinded treatment with alendronate or romosozumab for 1 year followed by unblinded alendronate; six cases with adjudicated AFFs were reported during the second year of the study (two in the romosozumab/alendronate group and four in the alendronate/alendronate group).[9] In the 7-year extension of the 3-year, placebo-controlled, clinical trial of the efficacy and safety of denosumab (a RANKL inhibitor), nine cases of ST/FS fractures were reported when all patients received active treatment, two of which were adjudicated as AFF – an incidence of 0.008/100 patient-years.[10] In addition, a single case of an adjudicated AFF was reported in the phase 3 FRAME clinical trial 3.5 months after romosozumab therapy, in a patient with prodromal symptoms before initiation of treatment.[11]

Odanacatib (ODN) is a cathepsin K (CatK) inhibitor with a unique mechanism of action that differs from that of bisphosphonates and denosumab, as it decreases bone resorption with only a transient reduction in bone formation marker serum procollagen type I N-terminal propeptide (P1NP).[12] The Long-Term Odanacatib Fracture Trial (LOFT) and its extension study (LOFT Extension) was a multicenter, phase 3, placebo-controlled clinical trial of the efficacy and safety of ODN, which was given orally once per week to more than 16,000 women with postmenopausal osteoporosis for up to 5 years.[13] The primary

hypothesis of LOFT and LOFT Extension was that treatment with ODN reduces the risk of morphometrically assessed vertebral fractures, clinical hip fractures, and clinical non-vertebral fractures compared to placebo.[14] All femur fractures were collected, and their location and specific radiographic features were identified by a Clinical Adjudication Committee (CAC) according to predefined criteria.[14] Thus, the study provided an opportunity to assess prospectively and under controlled conditions, with a predefined adjudication protocol, the incidence of ST/FS and AFF in postmenopausal women with osteoporosis treated either with placebo or ODN; there was no protocol-specified hypothesis for the analysis of AFFs.

Methods

Study design

The specific aims and detailed study design of LOFT and LOFT Extension (NCT00529373; EudraCT 2007-002693-66; Protocol Number 018) were previously reported.[13,14] In brief, this was a multinational (388 sites in 40 countries), randomized, double-blind, event-driven, placebo-controlled trial investigating the efficacy and safety of ODN in postmenopausal women with osteoporosis, enrolled during the period 2007–2009. In the prespecified, double-blind LOFT extension study, patients who completed LOFT on study medication and met additional entry criteria continued to receive treatment for up to a total of 60 months if they provided written informed consent.

At study enrollment, patients were randomized (1:1) to receive oral ODN 50 mg or placebo once per week, and weekly vitamin D_3 (5600 IU) and calcium supplements to ensure

a total daily intake of approximately 1200 mg. Patients underwent clinical assessments every 3 months during the first year and at 6-month intervals thereafter.

The study was conducted in accordance with principles of Good Clinical Practice, and was approved by the appropriate institutional review boards and regulatory agencies. All patients provided written informed consent.

Patients

Women ≥65 years of age were included in the study: without baseline radiographic vertebral fracture, and with total hip or femoral neck BMD T-score between -2.5 and -4.0; or with prior vertebral fracture and TH or FN T-scores between -1.5 and -4.0. Unless they were unable or unwilling to use available osteoporosis treatment, women were excluded if they had experienced prior hip fractures at any time or clinical fragility fractures within the prior 2 years, or if their BMD T-score was <-4.0 at either the TH or FN.

Assessment of clinical fractures

All clinical fracture events, except those of the skull, facial bones, fingers, and toes, were submitted to a fracture CAC composed of physicians based at the central evaluation site (Synarc/BioClinica, Newark, CA, USA), who were blinded to treatment assignments of the patients (see Supplemental File 1 for details of the procedure).

The anatomic location of confirmed fractures was determined, and fractures were classified as low-energy (consistent with energy less than or equal to a fall from standing height), stress fractures, traumatic, or pathologic (eg, malignancy, Paget's disease). When information was not conclusive, fractures were classified as having an unknown etiology. Adjudication occurred in two stages. Initially, a unanimous decision was required from three

CAC members (randomly selected from a panel of four) who each reviewed the data independently. If a unanimous decision was not reached, all four CAC members reviewed the case in a conference and a majority vote was required to confirm the fracture. The CAC classified the location of femoral fractures as hip (neck or intertrochanteric), femoral shaft (subtrochanteric or diaphyseal), or distal femur. ST/FS fractures were additionally evaluated for atypical radiographic and clinical features, and adjudicated as an AFF or ordinary ST/FS fracture according to both the 2010 and the updated 2013 ASBMR Task Force criteria.[1,2] Possible AFFs were discussed by all four CAC members.

Laboratory investigations

25-hydroxyvitamin D concentrations and the levels of the turnover markers C-terminal telopeptide of type 1 collagen and procollagen type 1 N-terminal propeptide were measured in serum obtained from patients with adjudicated AFFs after an overnight fast by previously reported methods;[14] carboxyterminal cross-linked telopeptide of type 1 collagen (1CTP) was measured by RIA (Synarc Labs, Lyon, France). BMD of hip and spine were measured by DXA, and vertebral fractures were assessed by spine radiographs.[14]

Data analysis

Patients who took at least one dose of study medication were included in the analysis. Time-to-first-event analyses used Kaplan–Meier estimates. Absolute fracture rates (patients and events per patient-year) were summarized. For femoral and hip fractures, treatments (ODN versus PBO) were compared using a Cox proportional hazard model with terms for treatment, stratum, and geographic region. Estimates of the hazard ratio (HR) and its 95% confidence

interval (CI) are provided. For ST/FS and AFF, estimates of the difference in rates per 100 patient-years are provided along with their 95% CI.

Pharmacogenetics

Details of pharmacogenetic analyses are provided in Supplemental File 2.

Results

Patients

Patient baseline characteristics, efficacy, and safety of ODN treatment were recently reported.[13] The mean (SD) age of the 16,071 evaluable participants was 72.8 (5.3) years, 68.5% were 70 years or older; 56.5% were Caucasian; and 46.4% had prior radiographically diagnosed vertebral fractures, the majority of which (59.3%) were mild (Genant Grade 1). Baseline mean (SD) BMD T-scores were: lumbar spine: -2.7 (1.2), TH: -2.4 (0.7), and FN: -2.7 (0.5). ODN and placebo groups were well matched at baseline and the mean (SD) period of observation was 44.7 (18.4) months and 43.8 (17.3) months in the ODN and placebo groups, respectively.

Femoral fractures

Three hundred and eight patients (1.9%) sustained a total of 324 femoral fractures, of which 296 fractures in 281 patients were adjudicated as low-energy (1.7% of patients) (Table 1). Fewer patients in the ODN group experienced a low-energy femoral fracture than in the placebo group (112 versus 169); the corresponding rates were 0.38 and 0.58/100 patient-years. The HR for low-energy femoral fracture was 0.65; 95% CI 0.51, 0.82; nominal $p<0.001$ (Table 2).

Hip fractures

Hip fractures were by far the most common type of fracture occurring in 87.7% of patients with femoral fractures, the large majority of which were low-energy. The rate of low-energy hip fractures was 0.29/100 patient-years in ODN-treated women and 0.56/100 patient-years in those treated with placebo. As reported in the primary manuscript,[13] the HR for low-energy hip fractures was 0.52; 95% CI 0.40,0.67; p<0.001 (Table 2). Baseline characteristics of patients with confirmed hip fractures were comparable between the ODN and placebo groups (Table 3).

ST/FS fracture

ST/FS fracture occurred in 10.7% of patients with femoral fractures, and nearly all were low-energy (30/33, 91%). Baseline characteristics of patients with ST/FS fractures are shown in Table 3. Differently from hip fractures, ST/FS fractures were more frequent in ODN-treated women than women treated with placebo (26 versus 7, respectively); the corresponding fracture rates were 0.087 and 0.024 per 100 patient-years for ODN and placebo groups, respectively. The estimated difference in rates per 100 patient-years for ST/FS fractures was 0.063; 95% CI 0.027, 0.106.

Distal femoral fractures

Distal femoral fractures occurred in only 3.6% of patients with femoral fractures, were predominantly low-energy, and occurred more frequently in the placebo group than in the ODN group (Table 1).

Cumulative incidence of femoral fractures

In the placebo group, the cumulative incidence of all first hip fractures alone or combined with ST/FS fractures increased progressively over time, while that of ST/FS fractures alone was low during the whole period of observation (Fig. 1A). In contrast, in the ODN group, there was a divergence of the curves of the combined cumulative incidence of hip and ST/FS fractures and of hip fractures alone, due mainly to an increase in the rate of ST/FS fractures (Fig. 1B). The cumulative incidence of non-pathological hip and ST/FS fractures combined or hip fractures alone in the ODN group was consistently lower than that of the placebo group (1.93% versus 3.11% for hip and ST/FS fractures combined; 1.53% versus 3.03% for hip fractures alone at Month 60). Time to first distal femoral fracture is not shown because of the very low incidence. The HR for non-pathological hip and ST/FS fractures combined was 0.62; 95% CI 0.49, 0.78; nominal $p<0.001$ (Table 2).

AFFs

In the 30 patients (24 in the ODN group, 6 in the placebo group) with low-energy ST/FS fractures, radiographs were evaluated by the CAC to determine if they met the criteria for an AFF. Of these, fractures were adjudicated as being consistent with an AFF in 10 patients (12 events) treated with ODN. None of the ST/FS fractures in placebo-treated women met the criteria of an AFF. The rate of adjudicated AFFs in the ODN group was 0.03/100 patient-years. Estimated difference in rates per 100 patient-years for AFF fractures was 0.03; 95% CI 0.02, 0.06. Clinical characteristics and laboratory findings of these 10 patients are summarized in Table 3, radiographs are shown in Fig. 2, and individual case descriptions are provided in Supplemental File 3. Mean (SD) age at baseline was 71.9 (4.4) years, 7 of these 10 women had prevalent vertebral fractures, baseline BMD was very low, particularly at the spine (mean T-score -3.88 [1.31]), and no patient had abnormally low serum alkaline

phosphatase values. These femoral fractures occurred between 7.2 months and 4.8 years (median 2.2 years) after starting ODN; four patients sustained the fracture within the first 2 years while in the other six patients, fractures occurred 2 to 5 years after initiation of treatment. In eight patients, the fracture followed a fall; in one patient (case 2 in Supplemental File 3), there was evidence of more than minimal trauma (the patient fell on the stairs and another woman fell on top of her). In the ninth patient (case 7), it was not clear whether the fracture followed or preceded the fall. Finally, the tenth patient (case 9), with no symptoms, had a stress fracture of the femoral shaft that was discovered incidentally on the image of the DXA (Fig. 3), and confirmed later by a radiograph, that showed a healing femoral shaft stress fracture with residual callus in the lateral cortex. Two patients (cases 1 and 6) sustained a second femoral shaft fracture of the contralateral femur after a fall. No patient was determined by the adjudication committee to have had prodromal symptoms suggestive of a stress fracture prior to the event.

Available baseline bone turnover marker values in women with adjudicated AFF were widely distributed from the lower end of the normal range to very high levels, indicative of high rates of bone turnover, and decreased by about 50% after 1 year of treatment with ODN (Fig. 4). This treatment-related response is in agreement with that observed with ODN treatment in the larger group of patients with and without fractures in the phase 2 study.[15] Consistent with the action of ODN on CatK, serum 1CTP values increased with treatment, suggesting good treatment compliance.

Fractures of the humerus

To obtain more insight into the pathogenesis of ST/FS fractures, we also studied the frequency and distribution of fractures of the humerus. The humerus is anatomically a long

bone, closely resembling the femur that is subjected, however, to different mechanical loads compared with the subtrochanteric region of the femur, which is subjected to the greatest loads in the body.[16] In addition, low-energy fractures of the humeral shaft with "atypical" radiographic characteristics have been infrequently reported in treatment-naïve or bisphosphonate-treated patients.[17,18] One hundred and sixty-three patients sustained a low-energy humerus fracture (108 in the placebo group and 55 in the ODN group). Similar to fractures of the femur, the majority were fractures of the proximal humerus (85.3%) with more fractures in the placebo group than in the ODN group (94 and 45, respectively) (Fig. 5). Distal fractures comprised 6.7% of all humeral fractures (eight in the placebo group and three in the ODN group), and 14 fractures were localized in the shaft of the humerus (8.6%; six in the placebo group and eight in the ODN group).

Pharmacogenetics

Results of the pharmacogenetic analyses are provided in Supplemental File 2.

Discussion

In contrast to the wealth of information about the incidence of hip fractures worldwide, there are limited data about the rates of ST/FS and the subset of AFFs from prospective controlled studies in women with postmenopausal osteoporosis. Yet, during the last decade, these fractures have been a focus of health professionals and the public due to the association of the latter with bisphosphonate use, the most widely used treatment for osteoporosis. We report here the rates of all femur fractures obtained prospectively, with predefined diagnostic criteria in a large randomized, controlled trial of a population of elderly women at increased fracture risk over 5 years. Our results confirm that in elderly women with osteoporosis, hip

fractures are by far the most common fractures of the femur; the rates of ST/FS and distal femur fractures are much lower, accounting for 10.7% and 3.6% of the total number of fractures, respectively. However, there were notable differences in the incidence of ST/FS among women receiving only calcium and vitamin D supplements and those who also received the CatK inhibitor, ODN. For this type of femoral fracture, rates were higher in ODN-treated women compared with rates in the placebo group. Moreover, all ST/FS fractures adjudicated as AFF were observed only in the women treated with ODN in our study. Our results raise questions not only about the mechanism(s) responsible for this discrepancy, but also reveal important issues relevant to the pathogenesis and diagnosis of AFF.

ODN, given orally once per week, was developed as treatment for osteoporosis that decreases bone resorption by about 55% but only transiently reduces bone formation, unlike bisphosphonates and denosumab. With ODN treatment, markers of bone resorption and bone formation decrease to nadir values during the first 6 months of treatment. Thereafter, the decrease in bone resorption markers generally persists for the whole duration of treatment while bone formation markers increase progressively towards baseline values.[13,15,19,20] Compared with placebo, once-per-week ODN reduced the risk of new/worsening morphometric vertebral fractures by 52%, clinical vertebral fractures by 67%, non-vertebral fractures by 26%, and hip fractures by 48%.[13] However, because of an observed increase in the risk of stroke in ODN-treated patients in the phase 3 study, further clinical development was stopped.[21] We believe that the results of the present study are not only of academic interest but provide novel insights into the currently unknown pathogenesis of AFF.

In the present study, the rate of low-energy hip fractures in women with osteoporosis recruited from five continents and treated with vitamin D and calcium was 0.56/100 patient-years, and decreased to 0.29/100 patient-years with additional ODN treatment. The rate of radiographically confirmed ST/FS fractures in the placebo group was 0.024/100 patient-years, lower than in most epidemiological studies, but it should be noted that the accuracy of the diagnosis of ST/FS obtained from ICD codes (as used in prior studies) is limited, and the addition or removal of a few cases can have a great impact on the result.[2] In contrast, women treated with ODN had a higher rate of confirmed ST/FS fractures (0.087/100 patient-years; 8.5% of all low-energy fractures of the femur), close to estimates of ST/FS reported in epidemiologic studies. In addition, 10 of the 24 cases of low-energy ST/FS fractures reported in ODN-treated patients were adjudicated as consistent with an AFF. Thus, treatment with ODN added to calcium and vitamin D was associated with increased rates of ST/FS, including those with atypical radiographic features.

The 10 patients with ST/FS fractures adjudicated as AFF described here had characteristics different from those described in the literature or seen in clinical practice in patients on long-term bisphosphonate treatment[6], as well as in patients with the rare bone disease pycnodysostosis, which is due to life-long deficiency of CatK.[22-26] In an analysis of 102 patients with bisphosphonate-associated AFF from the Quebec AFF registry, mean age was 69.5 years, mean BMD T-scores of lumbar spine and femoral neck were -1.6 and -1.6, respectively, only 34% occurred after a fall, and 71% of patients reported prodromal pain.[27] In contrast, patients who had adjudicated AFF in the LOFT trial had severe osteoporosis (mean lumbar spine BMD T-score -3.88, 70% with prevalent vertebral fractures), no prodromal symptoms, and nearly all fractures occurred after a fall. In addition, most patients showed no radiologic evidence of localized periosteal or endosteal thickening of the lateral

cortex at the fracture site. In the absence of the current definition of AFF, these fractures would have been diagnosed as common osteoporotic fragility fractures. Notably, whole exome sequencing in six of the 10 patients detected mainly coding variants found commonly in the general population (Supplemental File 2). These observations may suggest different mechanisms of development of these fractures in ODN-treated patients as compared to those fractures adjudicated as AFFs in bisphosphonate-treated patients. Stress fractures, considered the primary event in the initiation of an AFF, may have proceeded immediately to a complete fracture in the subset of subjects receiving ODN due to their severe osteoporosis at baseline, explaining the lack of prodromal symptoms and of radiographic/periosteal thickening of the cortex indicative of healing. In contrast, in patients with higher BMD (and strength), the bone could resist immediate progression of a stress fracture to a complete fracture, thus providing time for prodromal symptoms and endosteal/periosteal thickening of the cortex to develop. Therefore, the diagnostic criteria of AFFs, based largely on evidence obtained in association with bisphosphonate use, may not be applicable to other agents, such as ODN, and need to be reconsidered. Such need has also been suggested from other studies with bisphosphonates that showed that the way the angle of the fracture is assessed or the application of the 2010 or the 2013 criteria can lead to considerable differences in the diagnosis of AFFs.[28,29]

The low incidence of ST/FS compared to hip fractures, and the disparity between the absence of adjudicated AFF and the much higher incidence of hip fractures in women treated only with vitamin D and calcium compared to those treated with ODN, raise questions about the potential mechanism(s) underlying the possible differential action of ODN in different regions of the femur. Marked suppression of bone turnover has been frequently implicated in the pathogenesis of bisphosphonate-associated AFF.[2] Our results show that the magnitude of decrease of bone turnover markers after 1 year of ODN treatment was similar to previously

reported data with this agent, without abnormally low values. Notably, denosumab treatment, which decreases bone turnover to much lower levels than ODN, was associated with a reported lower incidence of adjudicated AFF (0.008/100 patient-years) in elderly women with osteoporosis treated for 10 years.[10] Moreover, recently reported bone biopsy results from the LOFT and LOFT Extension study showed that ODN treatment for 5 years preserved trabecular, intracortical, and endocortical remodeling and increased periosteal bone formation (modeling).[30] Thus, "oversuppression" of bone turnover cannot be implicated in the pathogenesis of the excess number of ST/FS fractures with atypical features observed during ODN treatment. It may be that ODN treatment alters the distribution of stresses in an already fragile femur by protecting the hip, resulting in more distal fractures of the shaft in women with severe osteoporosis. The proximal femur probably undergoes meaningful strengthening with therapy that mitigates strain in this region and reduces the risk of mechanical failure. Treatment may not cause a parallel strengthening of the subtrochanteric/diaphyseal region to the same extent or at the same rate as the proximal femur. Thus, the diaphysis would continue to experience high, or even relatively increased, tensile strain resulting in mechanical failure in individuals with reduced bone strength. Although the results of the distribution of fractures of the humerus, which as a long bone resembles the femur but due to its different stress loading has no obvious regions inherently vulnerable to fracture, are consistent with this notion, there are no other data available to test this hypothesis.

Other than the small number of AFFs, limitations of the present analyses include not having a preplanned protocol for collecting additional clinical information in patients with ST/FS fractures and not having baseline proximal femur radiographs. In addition, radiographs of femur fractures were obtained when these fractures occurred and not according to a

standardized protocol, sometimes making the assessment of diagnostic criteria of AFF, eg, periosteal/endosteal reaction, difficult.

While development of ODN for the treatment of osteoporosis was stopped, the results presented here illustrate that in patients at high risk for osteoporotic fractures, even an agent associated with adjudicated AFFs may have a favorable fracture benefit–risk balance. In addition, the study provides novel insights into the possible pathogenesis of AFF, suggesting that the current criteria for diagnosing these fractures may need to be reconsidered.

Disclosures

Socrates Papapoulos has received consulting and speaking fees from Amgen and UCB; and consulting fees from Gador and Radius Health.

Henry Bone has received research support and consulting fees from MSD; research support, consulting fees, and honoraria from Amgen and Shire; consulting fees and honoraria from Radius Health; and is a consultant for Entera Bio.

Felicia Cosman has received research grants from Amgen and Eli Lilly; is a consultant and advisor for MSD; and is a consultant, advisor, and speaker for Amgen, Lilly, and Radius.

David W. Dempster has received grants from Amgen, Eli Lilly & Co., and Radius Health; consulting fees from Amgen, Eli Lilly & Co., MSD, Radius Health ,and Tarsa; speaking fees from Amgen, Eli Lilly & Co., and Radius Health; and medical writing fees from Radius Health.

Michael R. McClung has received consulting fees and honoraria from Amgen and Radius Health.

Toshitaka Nakamura has received lecture/consultant fees from Asahi Kasei, Chugai, Daiichi Sankyo, and Taisho.

José Fernando Molina Restrepo has received consulting fees and honoraria from Amgen and Eli Lilly & Co.

Mary L. Bouxsein has received research funding from Radius Health; and speaker honoraria from Amgen.

Dosinda Cohn, Anne de Papp, Rachid Massaad, and Arthur Santora are current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, who may own stock and/or hold stock options in the company.

Acknowledgments

Socrates Papapoulos, Dosinda Cohn, and Anne de Papp accept responsibility for the integrity of the data analysis. All authors were involved in critically revising the article for important intellectual content and approved the final version for submission.

We would like to thank Paul Kostenuik for helpful discussions on the pathogenesis of femoral fractures and writing assistance, Keith Kaufman (Merck & Co., Inc., Kenilworth, NJ, USA) for research supervision and writing assistance, Gulum Kosova and Peter Shaw (Merck & Co., Inc., Kenilworth, NJ, USA) for data collection and pharmacogenetic analyses, and Boyd Scott (Merck & Co., Inc., Kenilworth, NJ, USA) for administrative and logistical support.

Editorial assistance, under the direction of the authors, was provided by Annette Smith of CMC AFFINITY, McCann Health Medical Communications, in accordance with Good

Publication Practice (GPP3) guidelines. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Data availability statement

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

References

1. Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010;25(11):2267-94.
2. Shane E, Burr D, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2014;29(1):1-23.
3. Nieves JW, Bilezikian JP, Lane JM, et al. Fragility fractures of the hip and femur: incidence and patient characteristics. Osteoporos Int. 2010;21(3):399-408.
4. Salminen S, Pihlajamaki H, Avikainen V, Kyro A, Bostman O. Specific features associated with femoral shaft fractures caused by low-energy trauma. J Trauma. 1997;43(1):117-22.

5. Rizzoli R, Akesson K, Bouxsein M, et al. Subtrochanteric fractures after long-term treatment with bisphosphonates: a European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group Report. Osteoporos Int. 2011;22(2):373-90.

6. Black DM, Abrahamsen B, Bouxsein ML, Einhorn T, Napoli N. Atypical Femur Fractures: Review of Epidemiology, Relationship to Bisphosphonates, Prevention, and Clinical Management. Endocr Rev. 2019;40(2):333-68.

7. Bilezikian J, Klemes A, Silverman S, Cosman F. Subtrochanteric fracture reports coincident with risedronate use. J Bone Miner Res. 2009;24(Suppl 1):S469. MO0354.

8. Black DM, Kelly MP, Genant HK, et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. N Engl J Med. 2010;362(19):1761-71.

9. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med. 2017;377(15):1417-27.

10. Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol. 2017;5(7):513-23.

11. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med. 2016;375(16):1532-43.

12. Duong le T, Leung AT, Langdahl B. Cathepsin K inhibition: a new mechanism for the treatment of osteoporosis. Calcif Tissue Int. 2016;98(4):381-97.

13. McClung MR, O'Donoghue ML, Papapoulos SE, et al. Odanacatib for the treatment of postmenopausal osteoporosis: results of the LOFT multicentre, randomised,

double-blind, placebo-controlled trial and LOFT Extension study. Lancet Diabetes Endocrinol. 2019;7(12):899-911.

14. Bone HG, Dempster DW, Eisman JA, et al. Odanacatib for the treatment of postmenopausal osteoporosis: development history and design and participant characteristics of LOFT, the Long-Term Odanacatib Fracture Trial. Osteoporos Int. 2015;26(2):699-712.

15. Bone HG, McClung MR, Roux C, et al. Odanacatib, a cathepsin-K inhibitor for osteoporosis: a two-year study in postmenopausal women with low bone density. J Bone Miner Res. 2010;25(5):937-47.

16. Goh SK, Yang KY, Koh JS, et al. Subtrochanteric insufficiency fractures in patients on alendronate therapy: a caution. J Bone Joint Surg Br. 2007;89(3):349-53.

17. Yavropoulou MP, Giusti A, Ramautar SR, Dijkstra S, Hamdy NA, Papapoulos SE. Low-energy fractures of the humeral shaft and bisphosphonate use. Journal of Bone and Mineral Research. 2012;27(6):1425-31.

18. Odvina CV, Levy S, Rao S, Zerwekh JE, Rao DS. Unusual mid-shaft fractures during long-term bisphosphonate therapy. Clinical endocrinology. 2010;72(2):161-8. Epub 2009/03/24.

19. Langdahl B, Binkley N, Bone H, et al. Odanacatib in the treatment of postmenopausal women with low bone mineral density: five years of continued therapy in a phase 2 study. J Bone Miner Res. 2012;27(11):2251-8.

20. Rizzoli R, Benhamou CL, Halse J, et al. Continuous treatment with odanacatib for up to 8 years in postmenopausal women with low bone mineral density: a phase 2 study. Osteoporos Int. 2016;27(6):2099-107.

21. Mullard A. Merck & Co. drops osteoporosis drug odanacatib. Nat Rev Drug Discov. 2016;15(10):669.

22. Hashem J, Krochak R, Culbertson MD, Mileto C, Goodman H. Atypical femur fractures in a patient with pycnodysostosis: a case report. Osteoporos Int. 2015;26(8):2209-12. Epub 2015/06/05.

23. Song HK, Sohn YB, Choi YJ, Chung YS, Jang JH. A case report of pycnodysostosis with atypical femur fracture diagnosed by next-generation sequencing of candidate genes. Medicine. 2017;96(12):e6367. Epub 2017/03/23.

24. Yates CJ, Bartlett MJ, Ebeling PR. An atypical subtrochanteric femoral fracture from pycnodysostosis: a lesson from nature. J Bone Miner Res. 2011;26(6):1377-9. Epub 2011/05/26.

25. Yuasa T, Maeda K, Kaneko K, Yoshikata K. Total Hip Arthroplasty after Treatment of an Atypical Subtrochanteric Femoral Fracture in a Patient with Pycnodysostosis. Case reports in orthopedics. 2015;2015:731910. Epub 2015/10/09.

26. Roth VG. Pycnodysostosis presenting with bilateral subtrachanteric fractures: case report. Clinical orthopaedics and related research. 1976(117):247-53. Epub 1976/06/01.

27. Morin S, Wall M, Belzile E, et al. Characterization of >100 patients with atypical femur fractures: the Quebec atypical femur fracture registry. J Bone Miner Res. 2017;32(Suppl 1):S4. 1015.

28. LeBlanc ES, Rosales AG, Black DM, et al. Evaluating atypical features of femur fractures: how change in radiological criteria influenced incidence and demography of atypical femur fractures in a community setting. J Bone Miner Res. 2017;32(11):2304-14.

29. Schilcher J, Koeppen V, Ranstam J, Skripitz R, Michaelsson K, Aspenberg P. Atypical femoral fractures are a separate entity, characterized by highly specific radiographic features. A comparison of 59 cases and 218 controls. Bone. 2013;52(1):389-92.

30. Recker R, Dempster D, Langdahl B, et al. Effects of Odanacatib on Bone Structure and Quality in Postmenopausal Women With Osteoporosis: 5-Year Data From the Phase 3 Long-Term Odanacatib Fracture Trial (LOFT) and its Extension. J Bone Miner Res. 2020;35(7):1289-99.

31. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics. 2009;25(14):1754-60.

32. Van der Auwera GA, Carneiro MO, Hartl C, et al. From FastQ data to high confidence variant calls: the Genome Analysis Toolkit best practices pipeline. Curr Protoc Bioinformatics. 2013;43:11.0.1-.0.33.

33. 1000 Genomes Project Consortium, Auton A, Brooks LD, et al. A global reference for human genetic variation. Nature. 2015;526(7571):68-74.

34. Lek M, Karczewski KJ, Minikel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016;536(7616):285-91.

Figure legends

Fig. 1. Kaplan–Meier curve of time to first hip or ST/FS fracture (low-energy, traumatic, or stress) with placebo (A) and ODN (B).

Fx = fracture; ODN = odanacatib; ST/FS = subtrochanteric/femoral shaft.

Fig. 2. Radiographs of ST/FS fractures in six different patients who received treatment with ODN; numbers correspond to the numbers of the patients with detailed descriptions in Supplemental File 3.

ODN = odanacatib; ST/FS = subtrochanteric/femoral shaft.

Fig. 3. Sequential DXA images of a patient who showed a stress fracture followed by periosteal healing. In this patient with severe osteoporosis and no symptoms (number 9 in Supplemental File 3), the stress fracture was incidentally discovered on DXA images.

Fig. 4. Biochemical markers in the serum of patients with AFF before and after 1 year of treatment with ODN. Dashed lines indicate normal ranges.

1CTP = carboxyterminal cross-linked telopeptide of type 1 collagen; AFF = atypical femoral fracture; BCE = bone collagen equivalents; Cr = creatinine; ODN = odanacatib; s = serum; u = urine.

Fig. 5. Number of patients and location of low-energy humeral fractures.

ODN = odanacatib

Table 1. Location and Etiology of Femoral Fractures (Hip, Shaft, and Distal Femur Fractures) Confirmed by Adjudication (Excluding Pathologic Fractures)

	ODN 50 mg qw		Placebo qw		Total	
	n	(%)	*n*	(%)	*n*	(%)
Patients in population	8043		8028		16,071	
with one or more femoral fractures	120		188		308	
with no femoral fractures	7923		7840		15,763	
Number of patients with[a]						
Femur fractures	120	(1.5)	188	(2.3)	308	(1.9)
Low-energy fracture	112	(1.4)	169	(2.1)	281	(1.7)
Stress fracture	2	(0.0)	0	(0.0)	2	(0.0)
Traumatic (high-energy) fracture	3	(0.0)	14	(0.2)	17	(0.1)
Fracture of unknown etiology	3	(0.0)	6	(0.1)	9	(0.1)
Hip fractures	91	(1.1)	179	(2.2)	270	(1.7)
Low-energy fracture	86	(1.1)	162	(2.0)	248	(1.5)
Stress fracture	1	(0.0)	0	(0.0)	1	(0.0)
Traumatic (high-energy) fracture	3	(0.0)	12	(0.1)	15	(0.1)
Fracture of unknown etiology	1	(0.0)	5	(0.1)	6	(0.0)
Femur, subtrochanteric, and shaft fractures[b]	26	(0.3)	7	(0.1)	33	(0.2)
Low-energy fracture	24	(0.3)	6	(0.1)	30	(0.2)
Stress fracture	1	(0.0)	0	(0.0)	1	(0.0)
Traumatic (high-energy) fracture	0	(0.0)	1	(0.0)	1	(0.0)
Fracture of unknown etiology	1	(0.0)	0	(0.0)	1	(0.0)
Distal femur and other locations[c]	4	(0.0)	7	(0.1)	11	(0.1)
Low-energy fracture	3	(0.0)	5	(0.1)	8	(0.0)
Stress fracture	0	(0.0)	0	(0.0)	0	(0.0)
Traumatic (high-energy) fracture	0	(0.0)	1	(0.0)	1	(0.0)
Fracture of unknown etiology	1	(0.0)	1	(0.0)	2	(0.0)

ODN = odanacatib; qw = once weekly.

[a]A patient with more than one femur fracture is counted once in each category; a patient experiencing more than one fracture in different locations appears in different relevant categories.

[b]"Shaft" indicates subtrochanteric/femoral shaft.

[c]"Other locations" includes location not specified.

Table 2. Cox Proportional Hazards Model for Time to First Fracture Confirmed By Adjudication (LOFT and LOFT Extension)

	Crude rate (per 100 patient-years)		ODN 50 mg qw versus placebo qw		
Fracture type	**ODN 50 mg qw**	**Placebo qw**	**Hazard ratio**	**95% CI**	**p-value**
Low-energy femoral fracture[a]	0.38	0.58	0.65	(0.51, 0.82)	<0.001[b]
Low-energy hip fracture[c] [13]	0.29	0.56	0.52	(0.40, 0.67)	<0.001
Non-pathological hip and ST/FS fractures[a]	0.39	0.63	0.62	(0.49, 0.78)	<0.001[b]

CI = confidence interval; ODN = odanacatib; qw = once weekly; ST/FS = subtrochanteric/femoral shaft.

[a]All-patients-as-treated population.

[b]The p-value should be interpreted as nominal and is provided to indicate the strength of the association, but not to confirm a hypothesis as it was performed as a post-hoc analysis.

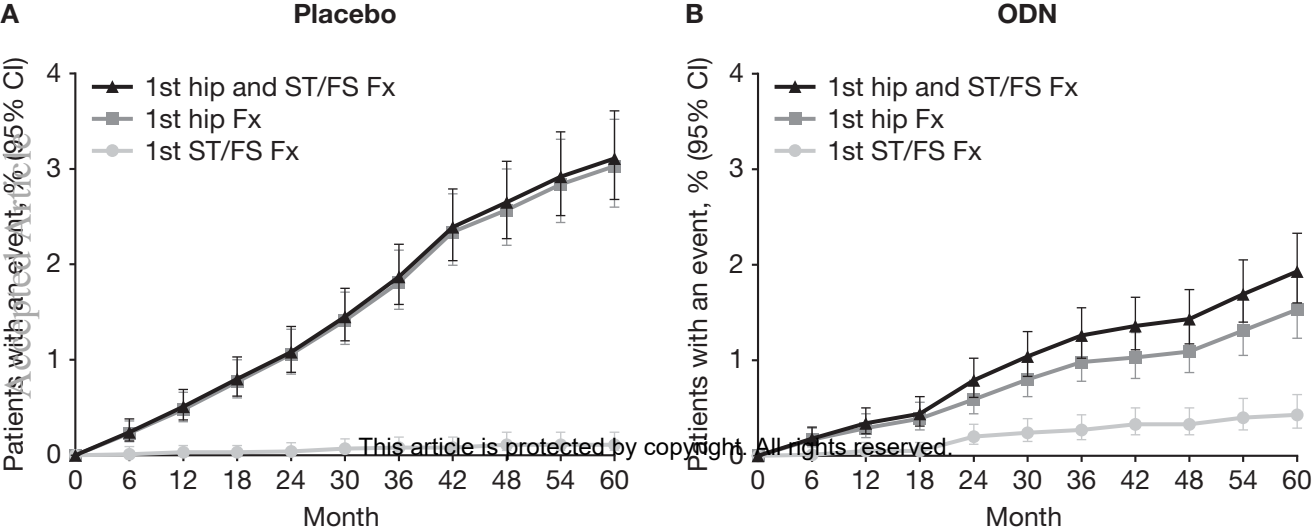
[c]Full analysis set.

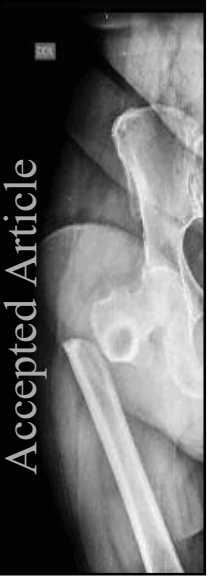
Table 3. Baseline Characteristics of Patients with Hip Fracture, ST/FS Fracture, and Adjudicated AFF

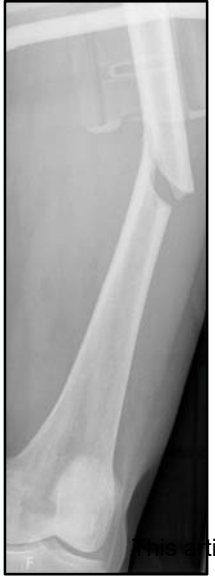
Baseline characteristic	Hip fracture		ST/FS fracture		AFF	ST/FS fracture excluding AFF
	ODN	Placebo	ODN	Placebo	ODN	ODN
	n = 91	*n* = 179	*n* = 26	*n* = 7	*n* = 10	*n* = 16
Age (years)	76.1 ± 5.7	75.0 ± 5.7	73.4 ± 5.2	70.3 ± 5.3	71.9 ± 4.4	74.4 ± 5.6
Years since menopause	29.3 ± 7.8	28.3 ± 8.5	26.8 ± 8.5	22.6 ± 9.8	25.3 ± 9.7	27.8 ± 7.9
Mean BMD T-score						
Lumbar spine	-2.55 ± 1.55	-2.35 ± 1.36	-2.95 ± 1.50	-1.74 ± 0.62	-3.88 ± 1.31	-2.39 ± 1.35
Total hip	-2.67 ± 0.71	-2.59 ± 0.70	-2.47 ± 0.76	-2.14 ± 0.97	-2.75 ± 0.78	-2.29 ± 0.72
Femoral neck	-2.78 ± 0.58	-2.81 ± 0.53	-2.79 ± 0.67	-2.62 ± 0.51	-2.97 ± 0.72	-2.68 ± 0.64
Prevalent vertebral fracture (%)	57.1	47.5	65.4	71.4	70.0	62.5

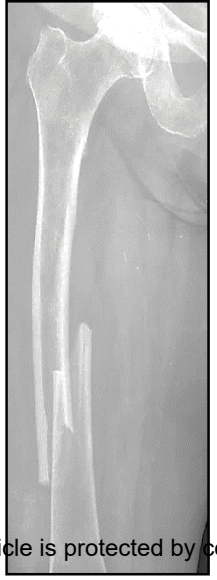
AFF = atypical femoral fracture; ODN = odanacatib; ST/FS = subtrochanteric/femoral shaft.

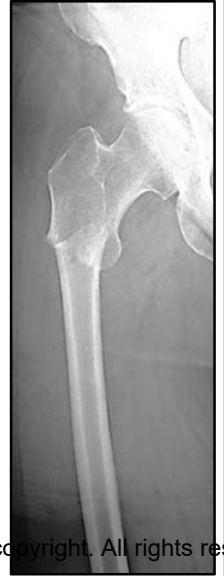
Data are mean ± SD unless stated otherwise.

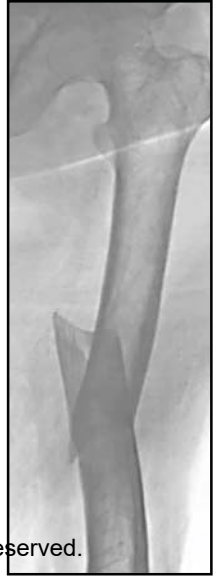


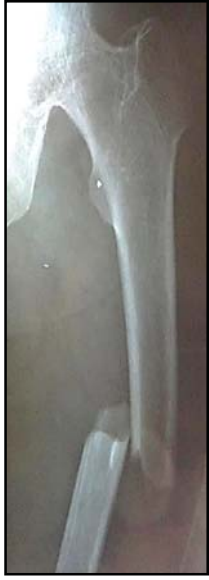




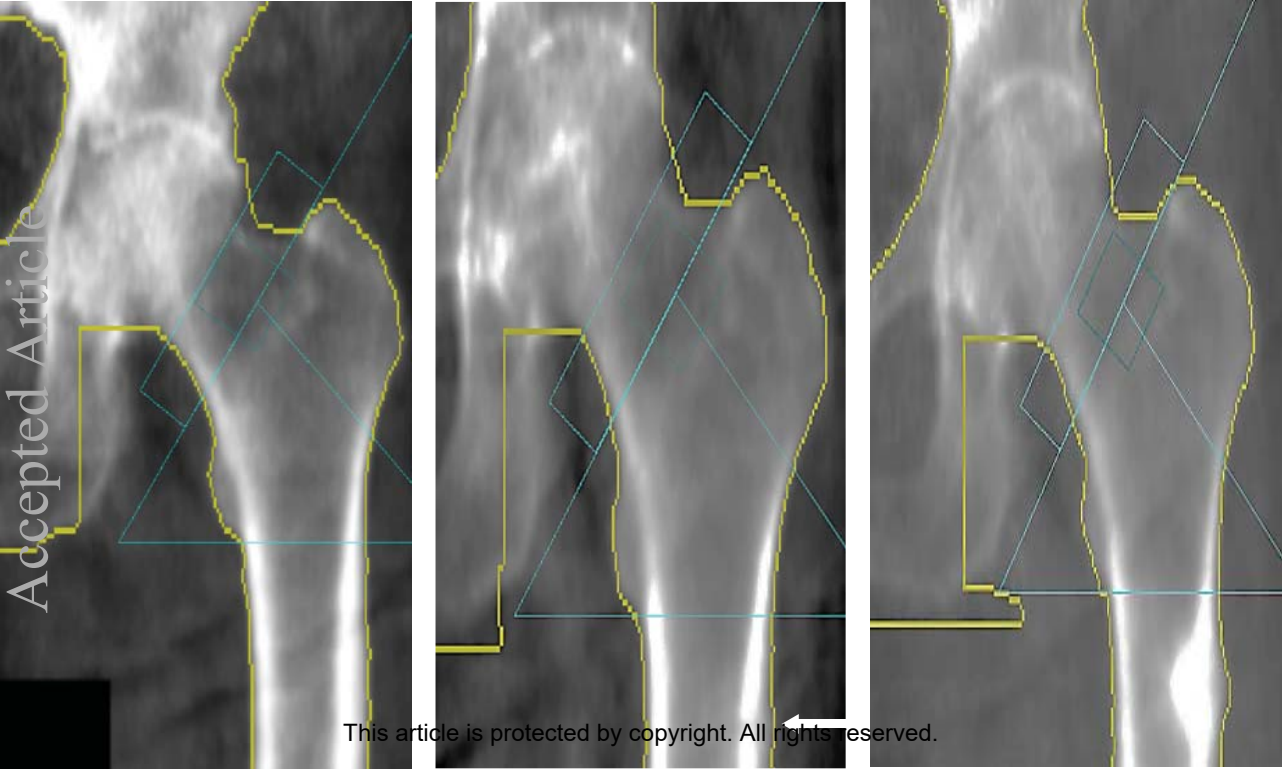




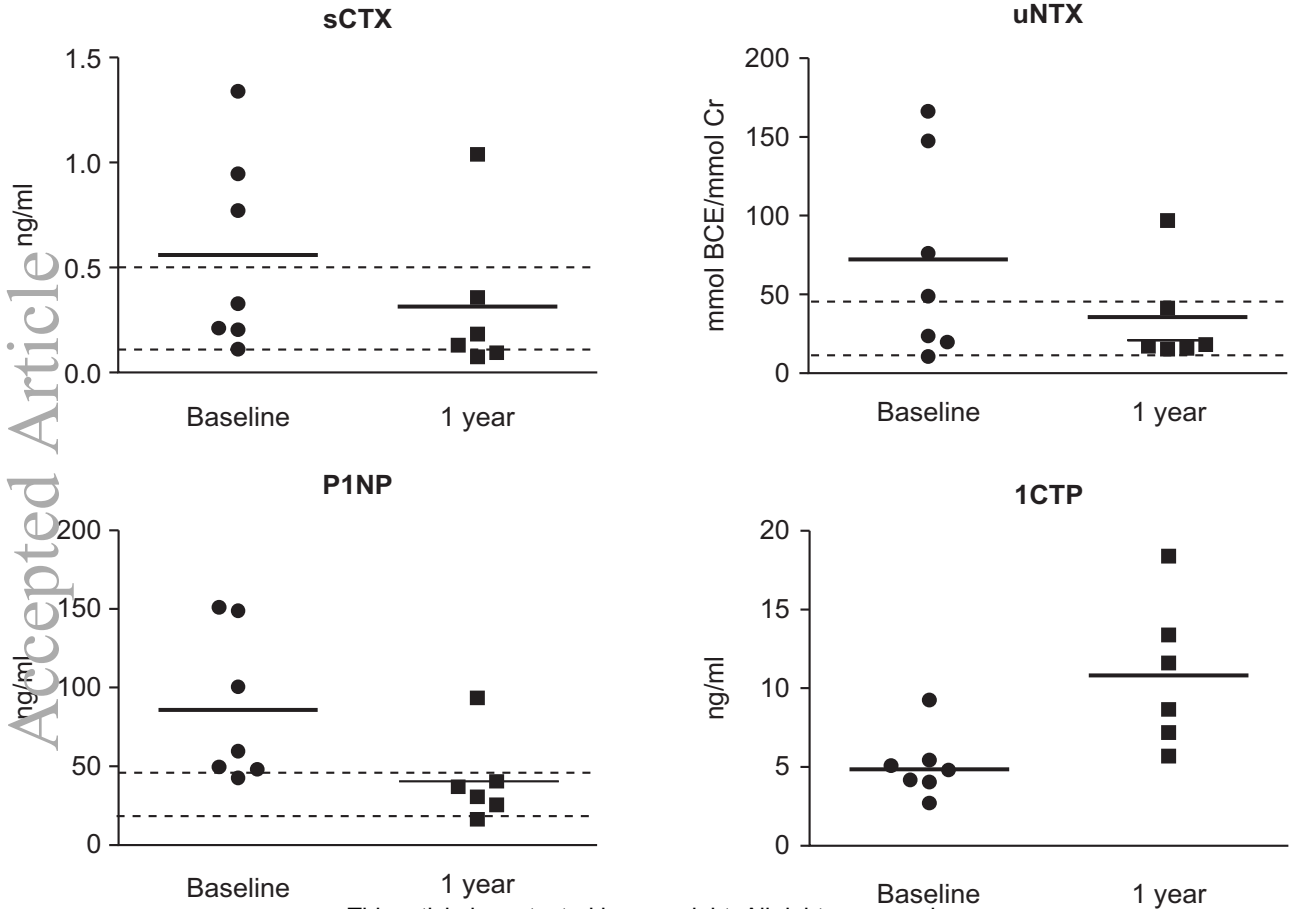




2 5 6 7 8 10



Baseline 2 years 3 years



Reference range premenopausal women