ORIGINAL ARTICLE

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Relationship Between Bone Mineral Density *T*-Score and Nonvertebral Fracture Risk Over 10 Years of Denosumab Treatment

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Abstract

Although treat-to-target strategies are being discussed in osteoporosis, there is little evidence of what the target should be to reduce fracture risk maximally. We investigated the relationship between total hip BMD *T*-score and the incidence of nonvertebral fracture in women who received up to 10 years of continued denosumab therapy in the FREEDOM (3 years) study and its long-term Extension (up to 7 years) study. We report the percentages of women who achieved a range of *T*-scores at the total hip or femoral neck over 10 years of denosumab treatment (1343 women completed 10 years of treatment). The incidence of nonvertebral fractures was lower with higher total hip *T*-score. This relationship plateaued at a *T*-score between -2.0 and -1.5 and was independent of age and prevalent vertebral fractures, similar to observations in treatment-naïve subjects. Reaching a specific *T*-score during denosumab treatment was dependent on the baseline *T*-score, with higher *T*-scores at baseline more likely to result in higher *T*-scores at each time point during the study. Our findings highlight the importance of follow-up BMD measurements in patients receiving denosumab therapy because BMD remains a robust indicator of fracture risk. These data support the notion of a specific *T*-score threshold as a practical target for therapy in osteoporosis. © 2019 The Authors Journal of Bone and Mineral Research published by Wiley Periodicals, Inc. on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: ANTIRESORPTIVES; DXA; FRACTURE RISK ASSESSMENT; OSTEOPOROSIS; TREAT TO TARGET

INTRODUCTION

For many chronic conditions, guidance is available regarding the attainment of specific clinical targets to minimize the risks associated with the disease. As examples, there are clear goals for blood pressure thresholds in patients with hypertension to reduce the risk of cardiovascular events, and specific goals for blood glucose and HbA1C levels to reduce the risk of

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complications of diabetes.[1,2] These goals have proven value in guiding treatment strategies to improve clinical outcomes.

Such goals have not been defined for the treatment of osteoporosis, which is considered successful when there is no significant loss of BMD and no new fracture events. This approach may be partly because of the limited capacity of most existing therapies to realize large improvements in BMD, a surrogate known to reflect bone strength. Attributing success to the lack of a negative clinical outcome, however, does not provide adequate guidance regarding the most appropriate therapeutic strategy to minimize fracture risk over time.

For treatment-naïve patients, specific (BMD) *T*-score thresholds are used to diagnose osteopenia and osteoporosis, and BMD is a robust predictor of fracture risk. Conversely, only a few studies have examined the extent to which the risk of fracture depends on the BMD achieved during treatment. After 3 years of annual intravenous zoledronic acid treatment in the HORIZON extension study, the subsequent fracture risk (both nonvertebral and vertebral) over 3 additional years was a function of BMD achieved after treatment.[3] In patients who achieved nonosteoporotic hip *T*-scores, future fracture risk was reduced the most. Similarly, after 5 years of oral alendronate treatment in the FLEX extension study, future fracture risk over the ensuing 5 years was a function of hip BMD.[4] In addition, *T*-scores achieved after 3 years of denosumab treatment in FREEDOM (A Study to Evaluate Denosumab in the Treatment of Postmenopausal Osteoporosis) determined the relative efficacy of continued treatment in year 4 and beyond.[5] These findings support the use of the *T*-score as an easily obtainable clinical variable to evaluate therapeutic success and the opportunity to stop or continue treatment.

Investigational and recently approved therapies, either alone or in combination, have led to large and continued gains in BMD,[6–9] thus a BMD target for osteoporosis treatment is relevant and of increasing interest. In this context, it has been proposed that potential targets for osteoporosis treatment could include achieving a *T*-score associated with acceptable fracture risk, with the caveat that such a *T*-score could vary depending on other risk factors, such as age, prior fracture history, and a propensity for falls. No consensus has been reached regarding what that *T*-score should be or which site—spine or hip—should be the basis for that potential target.[10,11]

Denosumab is a fully human monoclonal antibody that specifically binds RANKL to inhibit osteoclast formation, function, and survival. In the pivotal, 3-year FREEDOM trial in postmenopausal women with osteoporosis, denosumab significantly reduced bone turnover markers, increased lumbar spine and total hip BMD, and reduced new vertebral fractures, nonvertebral fractures, and hip fractures compared with placebo.[12] Importantly, the gains in total hip BMD explained a large proportion of the observed reduction in fracture risk.[13] Over 10 years of continued denosumab administration, long-term progressive increases in BMD resulted in an improvement of 21.7% at the lumbar spine, 9.2% at the total hip, and 9.0% at the femoral neck (all $P < 0.05$).[9,14–16]

The main objective of the current analysis was to determine the relationship between the incidence of nonvertebral fractures and total hip *T*-scores at the time of the fracture (while receiving denosumab treatment). In addition, we evaluated the proportion of patients who reached a given *T*-score at different time points. Ten years of continued denosumab therapy in the FREEDOM trial and its Extension (Extension Study to Evaluate the Long Term Safety and Efficacy of Denosumab in the Treatment of Osteoporosis) provide a unique opportunity to perform this analysis: Subjects with a wide range of total hip baseline *T*-scores were enrolled, and BMD increased in serial measurements obtained over time with continued denosumab treatment, allowing us to study the relationship between different *T*-scores achieved in response to treatment and subsequent 1-year incidence of nonvertebral fractures. Our findings underscore the importance of total hip *T*-score as a predictor of nonvertebral fracture risk during treatment for osteoporosis and provide additional insights into the use of BMD as a clinically relevant target for osteoporosis treatment.

MATERIALS AND METHODS

Study design

The study designs of the FREEDOM trial (NCT00089791) and its Extension (NCT00523341) have been published previously[9,12,14–16]; key methods are described in this report. In brief, the 3-year FREEDOM trial was a phase 3, multicenter, randomized, double-blind, placebo-controlled study conducted at 214 centers worldwide. Enrolled subjects were postmenopausal women between the ages of 60 to 90 years with a lumbar spine or total hip *T*-score < -2.5 at either site but ≥ -4.0 at both sites. Subjects were randomized to receive 60 mg of denosumab or placebo subcutaneously (s.c.) every 6 months for 3 years and took daily vitamin D (≥ 400 IU) and calcium (≥ 1 g) supplements.

Subjects who completed the 3-year FREEDOM trial, did not discontinue the investigational product, and did not miss > 1 dose were eligible to enroll in the Extension. During the Extension, all subjects were scheduled to receive open-label 60 mg denosumab s.c. every 6 months for 7 years with daily vitamin D and calcium supplements. Investigators and subjects were blinded to the BMD results throughout the 10-year study. The data reported here represent up to 10 years of denosumab exposure for women who received 3 years of denosumab in the FREEDOM trial and continued for up to 7 years in the Extension (long-term group) study.

Study subjects provided written consent. The study protocols were approved by the ethics committee or institutional review board at each site.

Study procedures and assessments

In the FREEDOM trial, subjects were evaluated every 6 months, and DXA measurements of the proximal femur were obtained every year for the 3-year duration. Subjects and investigators were blinded to the BMD results throughout the study. During the Extension study, study visits continued every 6 months for an additional 7 years. Over the 10-year total duration of observation (3 years in the FREEDOM and 7 years in the Extension trials), proximal femur DXA scans were evaluated for all subjects once per year from baseline to year 6, and thereafter at years 8 and 10. Subjects were asked about the occurrence of clinical fractures, including nonvertebral fractures,[12] at every scheduled visit, and they could also report clinical fractures at unscheduled visits. All fractures were adjudicated by a central imaging vendor (Synarc Inc., San Francisco, CA, USA) based on diagnostic imaging or a radiologist's report, as described previously.[12] Subjects' propensity to fall was not evaluated.

Statistical analyses

Total hip was chosen as the main site for this analysis because hip BMD is a more robust marker of nonvertebral fracture risk than spine BMD,[17,18] and it is less affected by artifacts, such as coexisting vascular calcification or osteoarthritic changes that could influence the BMD measurement. Nonvertebral fractures (excluding those of the skull, face, mandible, metacarpals, fingers, or toes) confirmed by the central imaging vendor were included in the analysis. Pathologic nonvertebral fractures and those associated with severe trauma (defined as a fall from a height higher than a stool, chair, or the first rung of a ladder; or severe trauma other than a fall) were also excluded from the analysis.

The relationship between total hip *T*-score and incidence of nonvertebral fractures and vertebral fractures through 10 years of denosumab therapy was analyzed post hoc, as follows: (1) a repeated-measures model (fitting observed *T*-scores against years on denosumab treatment at each BMD assessment, its quadratic term, and baseline *T*-score with random intercept and slope for each subject) was used to estimate each subject's *T*-score at specific time points during the entire follow-up period; (2) Cox's proportional-hazard model was fitted for time to first fracture with the corresponding estimated *T*-score for the subject at the time of the fracture and its quadratic term as time-dependent covariates; (3) the expected fracture risk during the entire follow-up period was estimated for various *T*-scores ranging from -3.0 to -0.5; and (4) the expected fracture risk at 1 year was extracted for each *T*-score to depict the *T*-score/fracture response curve. Baseline age (≥ 75 years versus < 75 years) and prior nonvertebral fracture status were evaluated separately as additional covariates in the Cox model. The significance of the reduction in 1-year nonvertebral fracture risk between pairs of *T*-scores that differed by an increment of 1.0 was assessed.

A sensitivity analysis of the relationship between total hip *T*-score and incidence of nonvertebral fractures for the first 3 years of the FREEDOM trial (denosumab and placebo arms) was also conducted.

Baseline values are reported using descriptive statistics. Because the exact timing of vertebral fractures was generally unknown, the date of the spine X-ray with confirmed vertebral fractures was used as a proxy for time to vertebral fracture.

The percentages of women with *T*-scores of > -2.5, > -2.0, and > -1.5 at the total hip or femoral neck at baseline and over 10 years of denosumab treatment were determined. The percentages of women with baseline *T*-scores of ≤ -2.5 at the total hip or femoral neck who attained a *T*-score > -2.5, > -2.0, and > -1.5 over time were also determined. The influence of baseline *T*-score on subsequent *T*-score improvement at each follow-up time point was also explored by grouping women based on baseline *T*-score quartiles.

RESULTS

Subject disposition and characteristics

A total of 3902 women were randomized to denosumab in the FREEDOM trial; of these, 2343 enrolled in the long-term denosumab group of the Extension study (Supplemental Fig. S1). The baseline characteristics of subjects in the FREEDOM and its Extension trials have been published.[9,12,14–16] Overall, 1343 women completed 10 years of denosumab treatment. Participant characteristics at the FREEDOM baseline and the FREEDOM Extension baseline for all subjects who received denosumab and for those who completed 10 years of denosumab treatment are shown in Table 1. The FREEDOM baseline characteristics of subjects who subsequently enrolled in the FREEDOM Extension were similar to those of all subjects who enrolled in the denosumab arm of FREEDOM. As expected, the mean baseline *T*-scores of subjects enrolled into the Extension study were higher than for the subjects who enrolled in the FREEDOM trial because of prior treatment intervention (either denosumab and/or calcium + vitamin D supplementation).

Relationship between total hip *T*-score and nonvertebral fracture

Overall, 373 subjects (10.3%) had nonvertebral fractures during denosumab treatment; 42 (1.2%) had hip fractures, and 155

Table 1. Participant characteristics at FREEDOM baseline and FREEDOM extension baseline: denosumab treatment

Parameter	Subjects Enrolled in FREEDOM (N = 3,902)	Subjects Enrolled in FREEDOM Extension (N1 = 2,343)	Subjects Enrolled in FREEDOM Extension (N1 = 2,343)	Subjects Who Completed 10 Years of Study (N2 = 1,343)
	FREEDOM Baseline		FREEDOM Extension Baseline	
Age, years	72.3 (5.2)	71.9 (5.0)	74.9 (5.0)	73.8 (4.6)
Age groups, n (%)				
≥ 70 y	2,872 (73.6)	1,672 (71.4)	1,974 (84.3)	1,073 (79.9)
≥ 80 y	322 (8.3)	144 (6.1)	325 (13.9)	154 (11.5)
Any prior fractures, n (%)				
Nonvertebral fractures	1,163 (29.8)	702 (30.0)	780 (33.3)	500 (37.2)
Vertebral fractures	929 (23.8)	559 (23.8)	573 (24.5)	385 (28.7)
Total hip *T*-score	−1.9 (0.8)	−1.9 (0.8)	−1.5 (0.8)	−1.4 (0.8)
Lumbar spine *T*-score	−2.8 (0.7)	−2.8 (0.7)	−2.1 (0.8)	−2.2 (0.8)
Femoral neck *T*-score	−2.2 (0.7)	−2.1 (0.7)	−1.8 (0.8)	−1.8 (0.7)

Data are expressed as mean (SD) unless otherwise noted.

N = number of subjects who were randomized to denosumab in FREEDOM.

N1 = number of subjects in FREEDOM who continued to receive denosumab in the FREEDOM Extension.

N2 = number of long-term denosumab-treated subjects who were still on study at the end of year 10.

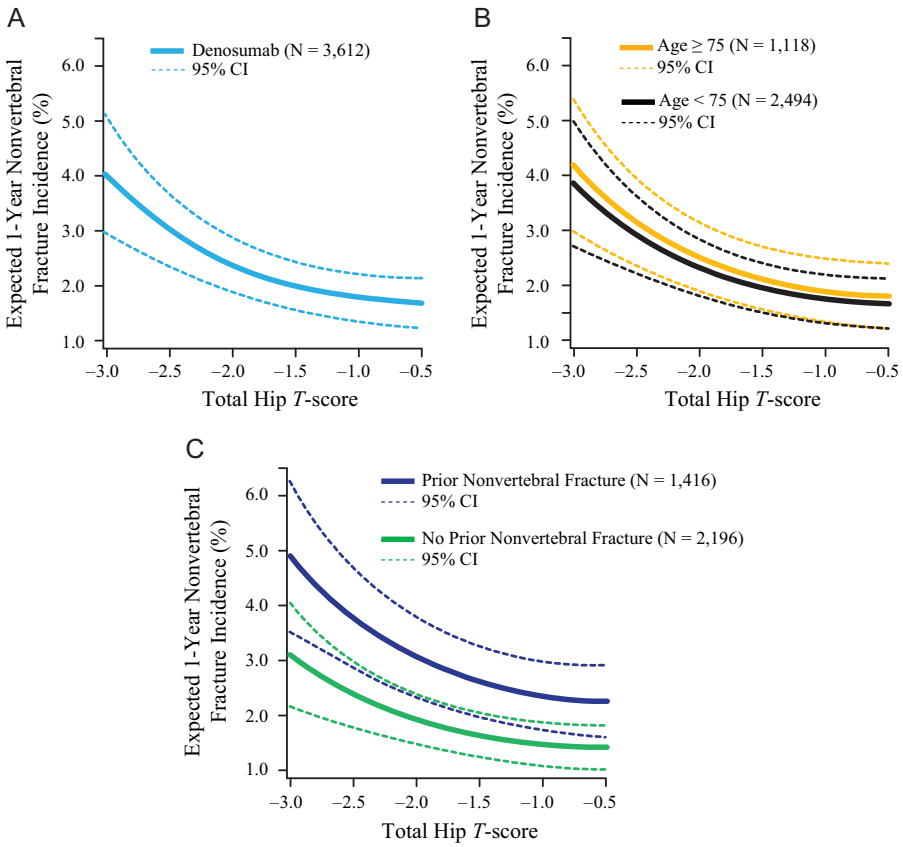

Fig. 1. Relationship between total hip *T*-score and incidence of nonvertebral fracture with up to 10 years of denosumab treatment (*A*) overall, (*B*) considering age, and (*C*) considering prior nonvertebral fracture. *N* = number of subjects randomized to denosumab in the FREEDOM study who had an observed total hip *T*-score at FREEDOM baseline and ≥ 1 observed total hip *T*-score during the FREEDOM or the Extension study. The 95% CIs are represented by dotted lines

(4.3%) had wrist fractures (Supplemental Table S1). The incidence of nonvertebral fractures and hip fractures was significantly lower among subjects who had at least one postbaseline total hip *T*-score of > -1.5 versus those who did not (9% versus 12% for nonvertebral fractures, and 0.5% versus 2% for hip fractures; $P < 0.0001$ for both).

There was an inverse relationship between the incidence of nonvertebral fractures and total hip *T*-scores attained during denosumab treatment (Fig. 1A). The 1-year nonvertebral fracture incidence was about 3.0% (95% CI, 2.3 to 3.7) in women with a total hip *T*-score of -2.5. In contrast, the 1-year nonvertebral fracture incidence was about 2.0% (95% CI, 1.5 to 2.4%) in women with a total hip *T*-score of -1.5. The relationship between attained total hip *T*-score and nonvertebral fracture risk reduction begins to plateau at a *T*-score between -2.0 and -1.5, above which fracture risk reductions are less robust with further increases in *T*-score. This relationship is further illustrated in Table 2, which shows the absolute nonvertebral fracture risk reductions after a 1.0 *T*-score unit increase for initial total hip *T*-scores between -2.5 and -1.5. For initial *T*-scores between -2.5 and -2.1, a 1.0 *T*-score unit increase was associated with a significant reduction in nonvertebral fracture risk (risk reductions ranged from 0.7% to 1.0%). In contrast, for initial *T*-scores between -2.0 and -1.5, the reduction in nonvertebral fracture risk was of lesser magnitude (0.3% to 0.6% risk reduction) and was no longer significant.

Table 2. Effect of initial total hip *T*-score on reduction in nonvertebral fracture risk.

Initial Total Hip *T*-score[a]	Total Hip *T*-score + 1[a]	Nonvertebral Fracture Risk Reduction	P-value
−2.5	−1.5	−1.01%	0.011
−2.4	−1.4	−0.91%	0.016
−2.3	−1.3	−0.83%	0.023
−2.2	−1.2	−0.75%	0.034
−2.1	−1.1	−0.67%	0.049
−2.0	−1.0	−0.60%	0.071
−1.9	−0.9	−0.54%	0.101
−1.8	−0.8	−0.48%	0.140
−1.7	−0.7	−0.42%	0.190
−1.6	−0.6	−0.37%	0.251
−1.5	−0.5	−0.32%	0.322

[a]Pairs of total hip *T*-scores differ by increments of 1.0.

Like the 10-year data, there was an inverse relationship between the incidence of nonvertebral fractures and total hip

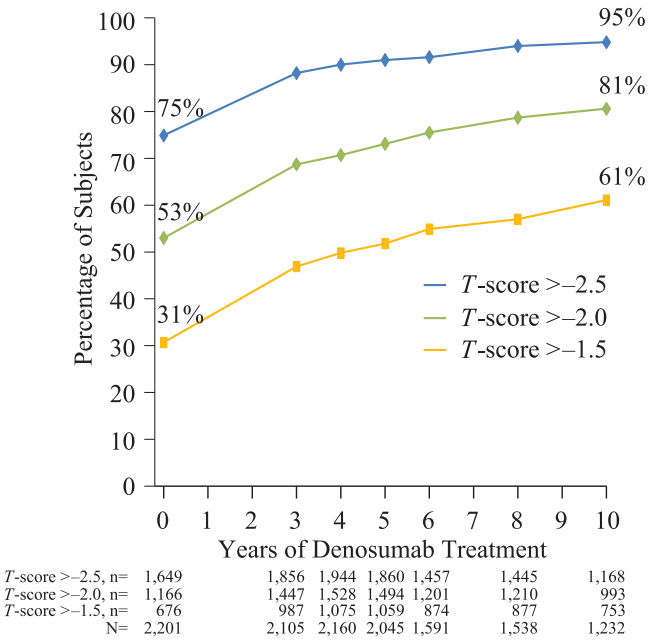

Fig. 2. Percentage of subjects with *T*-scores of > −2.5, > −2.0, and > −1.5 over 10 years of denosumab treatment. *N* = number of subjects randomized to denosumab in the FREEDOM study who had a baseline and at least one postbaseline *T*-score at the total hip; *n* = number of subjects with observed data at each time point

T-scores attained during treatment with denosumab and with placebo (Supplemental Fig. S2).

Absolute fracture risk was higher in older women and women with previous fractures for any *T*-score level; however, the inverse relationship between *T*-score attained and fracture risk reduction was maintained regardless of age (Fig. 1B) or prior nonvertebral fracture history (Fig. 1C). Additionally, the plateau seen in the relationship between higher *T*-score levels and fracture risk reduction was also maintained independently of baseline age and fracture history.

Analyses of the relationship between nonvertebral fractures and femoral neck *T*-scores and between vertebral fractures and total hip *T*-scores also showed a similar inverse relationship (Supplemental Figs. 3 and 4).

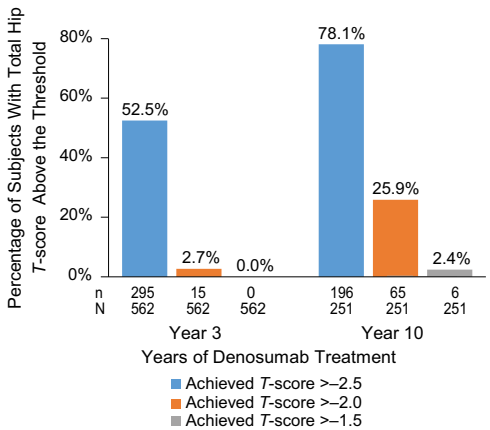

Fig. 3. Percentage of subjects with a total hip *T*-score ≤ −2.5 at FREEDOM baseline attaining *T*-scores of > −2.5, > −2.0, and > −1.5 after 3 and 10 years of denosumab treatment. *N* = number of subjects randomized to denosumab in the FREEDOM study and enrolled in the Extension who had a *T*-score of ≤ −2.5 at the total hip at FREEDOM baseline and an observed *T*-score at the time point of interest; *n* = number of subjects with a total hip *T*-score above threshold; BL = baseline

Proportion of women reaching a *T*-score threshold at year 10

In the current study of long-term denosumab subjects, the percentages of women with total hip *T*-scores of > -2.5, > -2.0, or > -1.5 progressively increased from 75%, 53%, and 31%, respectively, at FREEDOM baseline to 88%, 69%, and 47% after 3 years of denosumab treatment, and 95%, 81%, and 61% after 10 years of denosumab treatment (Fig. 2). In contrast, total hip *T*-scores of > -2.5, > -2.0, or > -1.5 were 73%, 50%, and 28% after 3 years of placebo (data not shown). The percentages of women with femoral neck *T*-scores of > -2.5, > -2.0, or > -1.5 also increased: from 67%, 39%, and 16% at FREEDOM baseline to 80%, 55%, and 29% after 3 years of denosumab treatment, and 89%, 69%, and 45% after 10 years of denosumab treatment (Supplemental Fig. S5).

More than one half of women with baseline *T*-scores of ≤ -2.5 at the total hip in the long-term denosumab group had attained a *T*-score of > -2.5 after 3 years of denosumab treatment, increasing to 78% after 10 years of treatment (Fig. 3). In this same group of subjects, 26% and 2.4% attained *T*-scores of > -2.0 and > -1.5 after 10 years of treatment respectively (Fig. 3). The percentage of subjects with baseline *T*-scores of ≤ -2.5 at the femoral neck who attained *T*-scores of > -2.5, > -2.0, or > -1.5 also increased over 10 years of denosumab treatment (Supplemental Fig. S6).

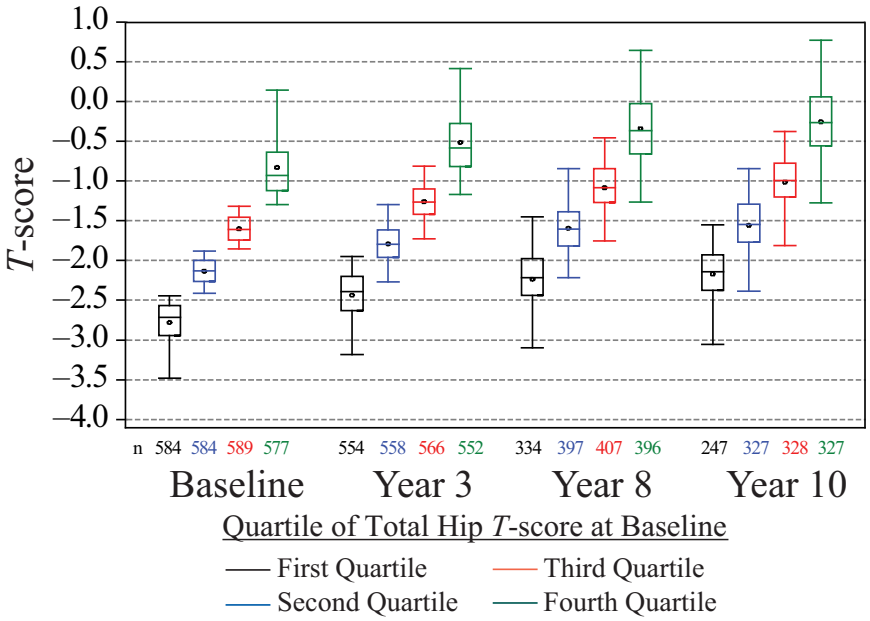

Fig. 4. Total hip BMD by quartile over time *T*-score over time by baseline total hip *T*-score quartile. Each box represents the respective baseline *T*-score quartile. The bottom and top of each box represent Q1 and Q3 *T*-scores within the respective baseline *T*-score quartile; the line within each box represents the median *T*-score; the dot represents the mean *T*-score

When subjects were grouped by their baseline total hip *T*-score quartile, each group had improvement in *T*-scores throughout 10 years of denosumab treatment, with higher *T*-scores at baseline more likely to result in higher *T*-scores at each time point (Fig. 4).

DISCUSSION

In this study, we have shown that a high proportion of subjects with osteoporosis achieved *T*-scores above the osteoporosis threshold (ie, *T*-score $\geq$ -2.5) with up to 10 years of continued denosumab treatment. The incidence of nonvertebral fractures decreased significantly as a function of the *T*-score achieved during therapy; this relationship was consistent across important demographic variables, such as age and prior fracture history, indicating that the absolute BMD attained on treatment is a key indicator of fracture risk. Within the relationship between total hip *T*-score and observed nonvertebral fracture risk, nonvertebral fractures began to plateau upon reaching a total hip *T*-score above -2.0 (associated with a 1-year nonvertebral fracture incidence of approximately 2%). A 1.0 *T*-score unit increase was associated with a significant reduction in fracture risk for *T*-scores up to, but not > -2.0, suggesting that a *T*-score threshold $\geq$ -2.0 would be an appropriate target for therapy to maximize treatment benefits. Further improvements in BMD were not associated with major additional changes in 1-year nonvertebral fracture incidence. The implication of this finding is that nonvertebral fracture risk may be maximally reduced if BMD *T*-scores above -2.0 are achieved and maintained, assuming an annual background rate of osteoporosis-related fracture of 1% to 1.5%.[19]

This is the largest long-term study of therapeutic intervention in the osteoporosis treatment setting to date and provides important insights into the relationship between absolute BMD and fracture risk among subjects receiving ongoing treatment with denosumab. It remains to be determined if similar conclusions can be made for other therapeutic agents that reduce fracture risk in patients with osteoporosis. However, for all approved therapies, preclinical data show that the relationship between BMD achieved on treatment and bone strength remains intact, thus it would be logical to infer that a similar relationship would be observed from clinical data. The Foundation for the National Institutes of Health Biomarkers Consortium Bone Quality Project is currently evaluating this relationship in pooled data from multiple clinical trials of osteoporosis agents.[20]

There is abundant evidence demonstrating a relationship between low BMD/*T*-score and increased risk of fracture in untreated postmenopausal women.[21–23] However, there is uncertainty regarding the strength of this relationship among patients receiving osteoporosis treatments. This may partly be explained by the relatively modest changes in *T*-score observed to date with most existing therapies (particularly in the hip); the small number of subjects from completed, long-term studies; and previous attempts to link fracture reductions with percentage change in BMD rather than the absolute BMD achieved while receiving different therapeutic agents.

A previous analysis of data from the FREEDOM trial demonstrated that change (gain) in BMD is a predictor of fracture risk reduction in patients treated with denosumab[13]; however, as demonstrated in the current study, absolute BMD achieved and corresponding *T*-score appear to be better predictors of fracture risk reduction. For example, for initial *T*-scores of between -2.5 and -2.1, a 1.0 *T*-score unit increase led to a significant reduction in nonvertebral fracture risk, whereas for initial *T*-scores of between

-2.0 and -1.5, the same incremental increase in *T*-score did not result in a significant reduction in nonvertebral fracture risk. We would like to point out, however, that this does not imply that patients with total hip *T*-scores > -2.0 who have prevalent fragility fractures or low spine BMD should not be treated.

Interestingly, associations between bone strength and a *T*-score threshold of approximately -1.5 have been observed in the treatment-naive population. In a study of untreated patients, hip fractures were almost exclusively observed among women with *T*-scores below -1.5, corresponding to an estimated strength (by CT finite element analysis) below 4000 Newtons.[24] A similar threshold was observed when the relationship between fracture occurrence and decreasing *T*-scores was evaluated in the National Osteoporosis Risk Assessment (NORA).[25]

The feasibility of treat-to-target (or goal-directed) strategies in the management of osteoporosis has been the subject of much debate.[26] Although there is currently no consensus on which parameter would best define the treatment target, the *T*-score has been proposed as the likely choice (along with the goal of freedom from fracture) based on the 2017 ASBMR Task Force on Goal-Directed Therapy in Osteoporosis. Specifically, a spine or hip *T*-score above -2.5 has been proposed for consideration by the task force because achieving a *T*-score of -2.5 (for patients initiating treatment with a *T*-score < -2.5) would reflect the patient having a BMD above the intervention and diagnostic threshold for treatment initiation in many guidelines.[26–29] Of note, the task force also suggests that therapy should be continued until a patient is fracture-free for 3 to 5 years, and that a higher *T*-score goal (ie, a *T*-score > -2.0) may be warranted in patients with a higher baseline risk, such as those over age 70 years or with a recent vertebral fracture. Our data, in addition to previously published results,[5] provide some evidence that achieving hip *T*-scores of at least -2.0 may help provide additional fracture reduction benefit, at least during treatment with denosumab.

Our data also suggest that a plateau in fracture risk is reached at similar BMD values independent of other risk factors such as older age and/or prevalent fracture. We acknowledge that the absolute background risk is not the same for every patient, which could justify different management strategies and goals for specific patients. If the goal is to minimize the fracture risk in every patient, however, a similar *T*-score value should be targeted regardless of those patients' characteristics. It is important to note that achieving a specific *T*-score threshold does not absolve patients or their physicians from further management strategies. The treating physician should consider appropriate treatment options to maintain gains in BMD, particularly in the context of reversible therapies, such as denosumab.

It is important to note that 10 years of denosumab treatment enabled a substantial proportion of women with baseline hip *T*-scores < -2.5 to achieve total hip non-osteoporosis *T*-scores, but only a small proportion achieved target total hip *T*-scores of > -1.5. The absolute level of *T*-score achieved and the degree of reduction in fracture risk over 10 years of denosumab treatment were dependent on both the baseline *T*-score and gains obtained over time. This is of clinical relevance as it implies that the baseline *T*-score would also provide valuable insight into the treatment strategy. For example, patients with very low total hip *T*-scores at baseline require larger gains in BMD and/or a longer treatment period to achieve a *T*-score associated with a low fracture incidence, thus additional strategies to realize larger and faster gains in BMD would be desirable. Investigational or recently approved therapies, such as sclerostin antibodies and parathyroid-related peptides, used alone, in sequence, or in combination with antiresorptives may result in better improvements in *T*-scores over shorter periods, resulting in faster reductions in fracture risk for patients with osteoporosis. Until recently, there was a lack of robust evidence demonstrating that strategies to achieve faster and/or larger gains in BMD would result in superior fracture reductions; the recently published results from the romosozumab ARCH trial now support this concept.[30]

Our study has several limitations. First, the FREEDOM patient population was postmenopausal and largely white, thus our findings may not be generalizable to other demographic groups. Second, spine BMD was not collected annually in all subjects in the FREEDOM trial. Third, only nonvertebral fractures were examined in detail. Fourth, it remains to be established whether the relationship between *T*-score and fracture incidence while on denosumab treatment can be extended to other osteoporosis therapies that have different mechanisms of action. For instance, teriparatide reduces nonvertebral fracture risk without substantial increments in hip BMD, which could pertain to its effects on cortical thickness and/or geometry. Analysis of existing data from other studies, such as that undertaken by the Foundation for the National Institutes of Health Biomarkers Consortium Bone Quality Project[23] could answer this question. In addition, there may be a question of bias from nonrandom enrollment in the Extension study and/or differential loss to follow-up during the Extension study. With regard to nonrandom enrollment in the Extension trial, among subjects who had received denosumab in the FREEDOM trial, the 1559 Extension nonparticipants had the same mean lumbar spine and total hip scores as the 2343 Extension enrollees.[31] The authors of that study also demonstrated that continued benefit from long-term denosumab treatment in the Extension study was not the result of a loss of subjects susceptible to fracture over time.[31]

In summary, our findings highlight the importance of the relationship between hip *T*-score and fracture risk, which is maintained during long-term therapy with denosumab. Regular monitoring of BMD during therapy may be useful to determine when fracture risk has reached a minimal threshold; treatment could therefore be suspended and/or consolidated (as in the case of a reversible therapy such as denosumab). Our observations support the concept of a treat-to-target (*T*-score) approach in osteoporosis. Further studies are needed to determine the most appropriate *T*-score level for each therapy and individual patient that could be utilized as the therapeutic intervention target.

Disclosures

SF: Consultancy for Amgen; Travel expenses from Amgen. CL: Former employee and stock/stock options of Amgen; Employment at and stock/stock options of UCB Pharma. CJFL: Former employee and stock/stock options of Amgen. AW, RBW: Employment at and stock/stock options of Amgen. JPB: Grants from Amgen, Eli Lilly; Consultancy for Amgen, Eli Lilly, Merck; Speakers' bureau of Amgen, Eli Lilly; Board membership of Amgen. FC: Grants from Amgen, Eli Lilly; Consultancy for Amgen, Eli Lilly, Radius Health, Tarsa Therapeutics; Speakers' bureau of Amgen, Eli Lilly, Radius Health; Educational presentations for Amgen, Eli Lilly, Radius Health; Advisory boards of Amgen, Eli Lilly, Radius Health, Merck. EC: Lecture fees from Amgen; Travel expenses from Amgen. LHG: Grant from CCBR Clinical Research. JM: Speakers' bureau of Amgen, Eli Lilly, Grunenthal; Travel expenses from Amgen, Eli Lilly, Grunenthal, Regeneron, Ono Pharmaceutical. JYR: Grants from IBSA-Genevrier, Mylan, CNIEL, Radius Health; Consultancy for IBSA-Genevrier, Mylan, Radius Health, Pierre Fabre; Lecture fees from IBSA-Genevrier,

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