Perspective

Theoretical Implications of the Biomechanical Fracture Threshold

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ABSTRACT: Because of the dichotomous nature of a bone fracture, when Φ , the ratio of the applied impact force to the bone strength, is greater than a critical value—the biomechanical fracture threshold—fracture should occur. We sought to elucidate the conceptual implications of this biomechanical fracture threshold with application to hip fracture. We used data from the PaTH study, a 2-yr clinical trial in postmenopausal women treated with alendronate, PTH, or their combination. Outcomes included the force applied to the hip in a sideways fall as estimated from subject height and weight; femoral strength as determined by QCT-based finite element analysis; the load-to-strength ratio Φ ; and total hip areal BMD from DXA. Results indicated that those with “very low” femoral strength (<2000 N) invariably had load-to-strength ratio Φ values well above the theoretical biomechanical fracture threshold ($\Phi = 1$), but those with “moderately low” femoral strength (2000–4000 N) displayed Φ values both above and below the theoretical biomechanical fracture threshold. This finding implies that the risk of a hip fracture can be high in those with only moderately low BMD because femoral strength can be low relative to fall impact forces. The observed weak correlation between areal BMD and the load-to-strength ratio Φ ($r^2 = 0.14$) suggests that consideration of the biomechanical fracture threshold may improve fracture risk assessment, particularly for those in the osteopenic range. Regarding treatment effects, only those subjects having load-to-strength ratio Φ values within a relatively narrow “transition zone” of $\pm 20\%$ of the assumed biomechanical fracture threshold at baseline were predicted to change fracture status during the trial. In theory, outcomes of fracture trials may be dominated by the responses of those within the “transition zone” at baseline, and treatment benefits in terms of fracture efficacy may depend the patient’s baseline status with respect to the biomechanical fracture threshold. We conclude that consideration of the theoretical implications of the biomechanical fracture threshold may lead to new insights and advances in the assessment and treatment of osteoporosis.

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INTRODUCTION

AS DICTATED BY fundamental principles of physics, if during a fall, the external force applied to a bone exceeds its strength, the bone will fracture; otherwise, fracture will not occur. Reflecting this dichotomous nature of a bone fracture, when the ratio Φ of the external force during a fall to the strength of the bone exceeds a value of 1.0, the biomechanical fracture threshold is exceeded and fracture should occur in the event of such a fall.^(1–3) Understanding the implications of the existence of such a biomechanical fracture threshold may provide insight into the etiology of osteoporotic fractures, assessment of fracture risk, noninva-

sive assessment and monitoring of treatment, and perhaps even design and interpretation of drug trials. It may also shed unique insight into such clinical paradoxes as to why small changes in areal BMD (aBMD) are associated with large reductions in fracture risk^(4,5) and why the –2.5 T-score “osteoporosis diagnosis” approach^(6,7) fails to identify the majority of those who eventually suffer a fracture.^(8–12)

Several recent clinical studies that computed load-to-strength ratios Φ at different skeletal sites have provided unique insight into age- and sex-specific fracture incidence,^(13–17) yet there has been limited discussion of the more general implications of a biomechanical fracture threshold. Rather than address the methodological issues of correctly estimating bone strength and load-to-strength ratios for individuals or what may be the best clinical technique to noninvasively measure bone strength—two important issues that are far beyond the scope of this article—our goal here is to focus instead on the conceptual implications of the existence of a biomechanical fracture threshold. This discussion is unique because it is the first to explore such

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broad clinical implications of the biomechanical fracture threshold, and it does so using illustrative data from state-of-the-art biomechanical analyses of patient-specific, clinical trial data.

For many of the following examples, we use data from a biomechanical analysis of subjects in the PaTH study. Described in detail elsewhere,^(18,19) the PaTH study was a multicenter, randomized, double-blind trial comparing the effects of PTH(1-84) versus alendronate versus a combination of the two in 238 postmenopausal, osteoporotic women (55–85 yr of age). For this discussion, the details of the treatment arms are not important, except to note that the study lasted 2 yr and both antiresorptive and anabolic treatments were used.

Subject weight and height were used to estimate the loads acting on the hip during such a sideways fall.^(20–22) QCT-based finite-element (FE) analysis, which has been used in orthopedic biomechanics research for well over a decade,^(23–32) was used to calculate the strength of the femur for a sideways fall configuration from the 3D QCT scans at baseline and 2 yr. Details of the specific FE analysis used here are presented elsewhere.⁽³³⁾ The load-to-strength ratio Φ was calculated as the ratio of estimated load applied to the femur to the FE-computed femoral strength, both for a sideways fall loading configuration. The higher the value of Φ , the greater the likelihood the bone will fracture under the assumed loading conditions, and indeed if all calculations were correct in an absolute fashion and a subject were to have a sideways fall, fracture would occur once the load-to-strength ratio exceeds a value of 1.0, the theoretical biomechanical fracture threshold. Because we aim to discuss the biomechanical fracture threshold in general rather than specific effects of any particular treatments, we describe here only 2-yr results for all treatments pooled for 166 subjects for which there was a complete set of QCT and DXA data. Outcomes discussed are the FE-predicted femoral strength, the load-to-strength ratio Φ , and total hip areal BMD (in g/cm²) as measured by DXA.

IMPLICATIONS FOR ASSESSMENT OF FRACTURE RISK

Importance of fall biomechanics for those with “moderately low” bone strength

A plot of the load-to-strength ratio Φ versus femoral strength for the PaTH cohort (Fig. 1) shows the expected $1/X$ relation. However, because of the combined effects of the nonlinear nature of this relation, the appreciable degree of scatter, and the distribution of the data with respect to the theoretical biomechanical fracture threshold, we found that those subjects having very low bone strength (<2000 N) also had load-to-strength Φ values much greater than this fracture threshold, that those with “moderately low” bone strength—in the range of 2000–4000 N—could have Φ values above or below the fracture threshold, and that those with bone strength above ~4000 N had load-to-strength ratios Φ below the fracture threshold. These data indicate therefore that there is a range of bone strength values in postmenopausal women—2000–4000 N in this analysis—for

FIG. 1. Baseline values of the load-to-strength ratio Φ plotted against femoral strength for a simulated fall to the side of the hip ($n = 166$). The moderate degree of scatter and the nonlinear nature of the relation indicates that subjects with “very low” bone strength (<2000 N) are highly likely to be above the theoretical fracture threshold (dashed line) but that subjects with “moderately low” bone strength (2000–4000 N) can fall above or below the fracture threshold.

which the risk of fracture may be difficult to assess from knowledge of bone strength alone. However, either above or below this range of bone strength values, the risk of fracture should be low or high, respectively, in the event of a sideways fall. In theory, for postmenopausal women with “moderately low” bone strength, the load-to-strength ratio may contribute to risk of fracture independently of bone strength.

Hip fractures and “osteopenia”

For the PaTH cohort of postmenopausal women, the average T-score for total hip BMD values was -1.90 (versus -2.5 for spine BMD and -2.2 for femoral neck BMD). Whereas T-scores from different sites can be used to classify osteoporosis, which can lead to different stratification of a cohort,^(34,35) for the purposes of this discussion, it is insightful to classify individuals as being osteoporotic or osteopenic based on the DXA total hip T-score.

Based on total hip T-scores, only 14% ($n = 23/166$) of the subjects in PaTH were “osteoporotic” (i.e., had total hip T-scores of less than -2.5), and 73% were “osteopenic” ($-2.5 < T < -1.0$). Among the osteoporotic subjects, 87% ($n = 20/23$) had Φ values >1 , the theoretical biomechanical fracture threshold (Fig. 2), which is a similar percentage to the 84% (102/121) among the osteopenic subjects. Assuming the risk of having a sideways fall does not depend on BMD, these data indicate that the majority of hip fractures will occur in the “osteopenic” subset of women because there are more subjects in that category and the proportion of subjects above and below the theoretical biomechanical fracture threshold was the same for osteoporotic and osteo-

FIG. 2. The weak but significant ($r^2 = 0.14$, $p < 0.001$) relation between Φ at baseline and areal BMD (total hip) at baseline ($n = 166$). The dashed line shows the theoretical biomechanical fracture threshold ($\Phi = 1$). The solid lines separate categories of osteoporotic (T-score < -2.5 ; $n = 23$), osteopenic ($-2.5 < \text{T-score} < -1.0$, $n = 121$), and normal (T-score > -1.0 , $n = 22$) patients, based on the T-score values of the total hip areal BMD values. Most individuals ($\sim 75\%$) in this cohort were above the theoretical biomechanical fracture threshold.

penic subsets. This finding is consistent with clinical data showing that most hip fractures occur in those classified as “osteopenic” by hip BMD.^(8–12) Analysis of the load-to-strength ratio data therefore provide a plausible explanation for why so many fractures occur in “osteopenic” individuals as defined by analysis of hip BMD; for many of these individuals, their bones are not strong enough to survive the impact from a sideways fall. The modest correlations between baseline values of aBMD and each of femoral strength ($r^2 = 0.49$; Fig. 3) and Φ ($r^2 = 0.14$; Fig. 2) further suggest that Φ may be a predictor of fracture risk independent of aBMD. This remains to be studied in prospective fracture trials for the hip, although such an effect has been observed in analysis of prevalent spine fractures.⁽³⁶⁾

IMPLICATIONS FOR ASSESSMENT OF TREATMENT EFFECTS: THE TRANSITION ZONE

Avoiding a discussion of the effects of any specific treatments, we now address the implications of the biomechanical fracture threshold for design of clinical trials and treatment of patients. In the following analysis, we pooled all treatment arms in the PaTH study and compared Φ for all subjects at baseline versus after 2 yr of treatment. Assuming a biomechanical fracture threshold value of $\Phi = 1.0$, we determined the number of subjects above and below the fracture threshold at the start and end of the study.

FIG. 3. QCT-based FE-calculated strength of the femur for a sideways fall versus total hip areal BMD by DXA ($n = 166$).

Outcomes of clinical trials may be dominated by a few subjects in the “transition zone”

Plotting Φ at the 2-yr follow-up versus Φ at baseline (Fig. 4) shows that all of the subjects who crossed the fracture threshold during the course of this trial were within what we have termed a “transition zone” of the fracture threshold at baseline (i.e., $0.8 < \Phi < 1.2$). The width of this transition zone was independent of the assumed value of the biomechanical fracture threshold. One implication of this transition zone is that, even if a treatment substantially increased bone strength for a particular subject during the course of a trial and thus reduced their load-to-strength ratio Φ , if that subject were not within the transition zone at the start of the trial, they would not cross the fracture threshold during the trial and would still be expected to fracture if exposed to a sideways fall. Biomechanical theory therefore dictates that, overall, subjects having baseline Φ values outside the transition zone may have little influence on the outcome of a limited-duration clinical trial. Equivalently, the outcome of a fracture trial may be dominated by the subset of subjects whose Φ scores at baseline are relatively close to the biomechanical fracture threshold (i.e., by those within the transition zone). In the PaTH study, despite a variety of therapeutic interventions—including placebo, antiresorptive, and anabolic therapies, alone and combination—the transition zone was quite narrow. This suggests that the width of the transition zone may be quite narrow in general, although it will depend also on the duration of the trial and potency of the therapy.

Small changes in bone strength can have a marked effect on fracture risk and outcomes of clinical trials may be determined by a small proportion of individuals

In theory, if the strength of the femur in a fall loading condition was 2400 N, if 2500 N of external force was de-

FIG. 4. Plot of Φ at baseline vs. Φ at 24-mo follow-up ($n = 166$). Data from the PaTH cohort, all treatments pooled, simulated fall to the side of the hip. Values below the $Y = X$ line show a positive benefit of treatment on bone strength. During the course of the trial, subjects in the indicated boxes moved either below or above the theoretical biomechanical fracture threshold (assumed value $\Phi = 1.0$ shown with dashed lines). All such subjects had baseline Φ values within a “transition zone” range of about 0.8–1.2. Altogether, there were 77 subjects within the transition zone at baseline.

oretical biomechanical fracture threshold ($\Phi = 1$) at baseline. If in reality, many in a trial are so close to their biomechanical fracture threshold—as invariably some will be—small changes in the bone strength of these subjects could have large effects on their likelihood of fracture in the event of a sideways fall. Moreover, once a person has increased their bone strength sufficiently to cross above the biomechanical fracture threshold, increasing their bone strength further may not afford greater fracture protection for that type of fall (although it could confer an advantage for more severe falls). This concept explains the clinical finding that a range of increases in aBMD with drug therapy was associated with relatively similar reductions in fracture risk.⁽³⁷⁾

The proportion of subjects in PaTH above the theoretical biomechanical fracture threshold (i.e., those who would be predicted to fracture if exposed to a sideways fall) decreased from 75% at baseline (124/166) to 69% (114/166) after 2 yr of treatment, an absolute difference of 6% (Table 1). Considering those only in the transition zone at baseline, the corresponding proportions were 53% (41/77) above the fracture threshold at baseline and 40% (31/77) at 2 yr, an absolute difference of 13%—about twice that when the full cohort is considered. The 2-yr increases in aBMD by DXA (~2.9%) were the same in the full cohort and transition zone subset (Table 1). If changes between baseline and follow-up in the proportion of those above the biomechanical fracture threshold are related to changes in clinical fracture efficacy—realizing of course that analysis of clinical fracture efficacy requires a placebo group—these data may

TABLE 1. NUMBER AND PROPORTION (EXPRESSED AS A PERCENTAGE) OF SUBJECTS HAVING $\Phi \geq 1.0$ AT BASELINE AND AT 24-MO FOLLOW-UP AND ABSOLUTE CHANGES IN THOSE PROPORTIONS

	Number (percent) of subjects having $\Phi \geq 1.0$		Percent change over 24 mo			
	Baseline	24 months	Number of subjects having $\Phi \geq 1.0^*$	Φ	Femoral strength	aBMD
Full cohort ($n = 166$)	124 (74.7%)	114 (68.7%)	6.0%	-3.47 ± 10.3	4.79 ± 11.4	2.82 ± 4.74
Within TZ ($n = 77$)	41 (53.2%)	31 (40.3%)	12.9%	-2.24 ± 9.94	3.36 ± 10.8	2.97 ± 4.88
Outside TZ ($n = 89$)	84 (94%)	84 (94%)	0%	-4.53 ± 10.6	6.02 ± 11.7	2.69 ± 4.65

Also shown are percent changes (mean $\pm$ SD) in Φ , FE-calculated bone strength, and DXA-measured areal BMD (aBMD, total hip). All percent changes are for 24-mo follow-up with respect to baseline for the PaTH cohort with all treatments pooled. Results are presented for the full cohort ($n = 166$), those only within the transition zone ($0.8 \leq \Phi \leq 1.2$ at baseline, $n = 77$), and those only outside the transition zone ($n = 89$).

* Absolute change in percent between baseline and 24 mo.

TZ, transition zone.

veloped during such a fall, that individual would fracture because the external force would exceed the bone strength and Φ would exceed the fracture threshold ($\Phi = 1.04 > 1.00$). Hypothetically, if this patient's bone strength increased with a treatment by 5% from 2400 to 2520 N, for the same fall, they would no longer fracture because Φ would now be (just) less than the fracture threshold ($\Phi = 0.99 < 1.00$). With this in mind, the fairly wide distribution of Φ in a typical osteoporotic cohort such as PaTH dictates that small changes in bone strength in just a small proportion of individuals—those in the transition zone at baseline who are clustered nearby the fracture threshold—may greatly influence the outcome of a fracture trial. The data from the PaTH study indicate that ~12% of that cohort (20 of the 166 individuals analyzed) was within $\pm 5\%$ of the assumed the-

explain in part why post-hoc analysis of subsets of patients in clinical trials can show significant antifracture efficacy that was not apparent when the entire trial cohort was considered together.^(38–42) Furthermore, these data also explain how different fracture reduction rates can be associated with the same mean changes in aBMD (or bone strength) depending on the distribution of baseline Φ in the cohort.

Implications for the design of clinical trials and who to treat

The biomechanical fracture threshold also has implications for design of clinical trials intended to show antifracture efficacy of a given intervention. One approach suggested by the concept of a transition zone is to screen for Φ at baseline and only enroll those subjects who are within the

transition zone. Based on the data presented here for the PaTH trial, that would result in selection of about one half (77 of 166 subjects) of a traditional osteoporotic cohort if using the same entry criteria as used in PaTH. As discussed above, this approach should lead to a higher measure of fracture efficacy because the fracture outcome of those subjects in the transition zone should be more sensitive to treatment than those outside the transition zone. Such a streamlined cohort may therefore provide a more statistically powerful design for detecting treatment effects and presumably for directly comparing effects of different treatments. This would lead to substantial time and cost savings, making the overall drug development process more efficient.

One possible concern with such an approach is that this selection process for a clinical trial may bias the cohort in some way, particularly in terms of well-accepted BMD selection criteria, such as used in PaTH. However, the data in Fig. 2 indicate that this is not a concern, at least not if the transition zone is determined by FEA of QCT scans. This is because of the weak correlation between FE-calculated values of Φ and total hip BMD; thus, selecting a subset based on a range of Φ values should not bias the BMD selection. Another potential concern is related to the distinction between the optimal cohort to show efficacy versus that needed to establish external validity, which may be critical for these sorts of screening strategies. According to theory, showing efficacy for those outside the transition zone would be expected to be challenging—not because the treatment does not improve bone density and strength, but simply because there would be insufficient time in the trial for those with initially high Φ values to fall below the biomechanical fracture threshold.

Related, the data in Fig. 4 suggest that a treatment of an individual patient could work very well in terms of increasing bone strength but could fail to protect them against fracture if they were too far from the transition zone at the start of treatment. In making decision treatments for patients, such issues might be considered in the future, as well as BMD (or strength) and other known risk factors for fracture, particularly age, sex, and history of prior fracture.^(6,12,43–46) Consider two patients with the same low bone strength and high value of Φ , above the fracture threshold. A younger patient with such characteristics may move below the biomechanical fracture threshold given enough time on treatment, but a patient with a short life expectancy might never cross below the fracture threshold no matter how well their bones responded to treatment. We emphasize that this type of analysis has not been validated in terms of predicting changes in fracture outcome with treatment and thus should only be considered as theoretical at this juncture.

DISCUSSION

In this perspective, we introduce and discuss the implications of a biomechanically based fracture threshold. We recognize that clinically it will likely never be possible to exactly predict, for an individual, the forces that will develop during a future fall or to exactly measure the associ-

ated strength of the individual's bone in response to that particular type of fall, should that fall actually occur. Thus, whereas in theory, the biomechanical fracture threshold has a value of $\Phi = 1.0$ when the fall force and bone strength are both known with certainty, in practice, no surrogate endpoint for fracture will display such sharply defined thresholds as discussed here. Rather than address the challenging methodological issues associated with achieving the latter in a clinical context, we sought instead to explore more conceptually the theoretical implications of the existence of the biomechanical fracture threshold.

The general nature of the issues discussed here should be quite robust to the assumed value of $\Phi = 1.0$ for the biomechanical fracture threshold and to the precise methods used to generate the example data. Even so, we caution that there are no accepted standards for noninvasive measurement of either bone strength or in vivo loads applied to bones during falls, and thus none of the specific values of bone strength or load-to-strength ratio presented here should be considered in absolute terms. The PaTH study was not designed with adequate power to study fracture outcomes, and indeed there was only one hip fracture in the study, and this individual was not in the QCT-FE subset. Thus, although the biomechanical fracture threshold awaits validation from prospective fracture outcome studies, the theory does provide plausible explanations for many poorly understood issues: (1) why most of those who suffer hip fractures are classified as “osteopenic” by BMD criteria; (2) why small increases in BMD can be associated with appreciable fracture efficacy without relying on considerations of “bone quality”; and (3) why fracture efficacy as measured in a clinical trial can depend on the baseline fracture risk status of the cohort. In addition, Φ -based biomechanical analyses of age- and sex-related fracture patterns for various cohorts provide results that are more consistent with observed incidence rates than when only BMD is used for such purposes.^(14–17) Recent analyses of prevalent spine fractures⁽³⁶⁾ and incident hip fractures⁽⁴⁷⁾ are also supportive of the Φ -based approach. The specific approach used here to show the implications of the biomechanical fracture threshold should therefore not be considered as complete but rather a basis for more thorough development and innovation. Even so, it is hoped that this biomechanical perspective provides some new insight into a number of issues related to the clinical management of osteoporosis.

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