Published in final edited form as:

Curr Opin Pharmacol. 2014 June ; 0: 64–71. doi:10.1016/j.coph.2014.03.006.

Are we taking full advantage of the growing number of pharmacological treatment options for osteoporosis?

Karl J. Jepsen, Stephen H. Schlecht, and Kenneth M. Kozloff

Department of Orthopaedic Surgery The University of Michigan Biomedical Science Research Building 109 Zina Pitcher Place Ann Arbor, MI 49109 USA

Abstract

We are becoming increasingly aware that the manner in which our skeleton ages is not uniform within and between populations. Pharmacological treatment options with the potential to combat age-related reductions in skeletal strength continue to become available on the market, notwithstanding our current inability to fully utilize these treatments by accounting for an individual's unique biomechanical needs. Revealing new molecular mechanisms that improve the targeted delivery of pharmaceuticals is important; however, this only addresses one part of the solution for differential age-related bone loss. To improve current treatment regimes, we must also consider specific biomechanical mechanisms that define how these molecular pathways ultimately impact whole bone fracture resistance. By improving our understanding of the relationship between molecular and biomechanical mechanisms, clinicians will be better equipped to take full advantage of the mounting pharmacological treatments available. Ultimately this will enable us to reduce fracture risk among the elderly more strategically, more effectively, and more economically. In this interest, the following review summarizes the biomechanical basis of current treatment strategies while defining how different biomechanical mechanisms lead to reduced fracture resistance. It is hoped that this may serve as a template for the identification of new targets for pharmacological treatments that will enable clinicians to personalize care so that fracture incidence may be globally reduced.

Introduction

A common goal for the pharmacological treatment of osteoporosis is to reduce fracture incidence. Most treatments have been centered on improving bone mineral density (BMD), which is a non-invasive measure of bone mass. This is an appropriate place to begin given that DEXA is a commonly available technology used to screen individuals for osteoporosis and because most pharmacological treatments have traditionally centered on slowing age-related bone loss [1]. However, we have known for quite some time that osteoporosis is not

© 2014 Elsevier Ltd. All rights reserved.

Corresponding Author Karl J. Jepsen, PhD Glancy Family Scholar Department of Orthopaedic Surgery University of Michigan 109 Zina Pitcher Place Ann Arbor, MI 48109-2200 USA kjepsen@umich.edu +1-734-763-2648.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

simply a bone loss disease [2-4], but that there are many age-related changes in bone structure and composition that contribute to the gradual decline in fracture resistance (Figure 1). As the number of pharmacological treatment options steadily increases and as research provides greater insight into skeletal aging, there will be new opportunities for developing the technologies and scientific approaches which will enable physicians to treat individuals in ways that will improve bone strength more strategically. The physician currently has pharmacological treatment options that target bone loss, bone gain, or both (Figure 2). How does the physician decide which of these options should be used to most effectively treat each individual patient for low bone mass? Surprisingly, the introduction of new pharmacological treatment options has surpassed our ability to differentially diagnose and treat individuals based on their individual pathway to fracture susceptibility (Figure 1). This is a major problem because it means that we may not be taking full advantage of the treatments currently available or in the pipeline. Current pharmacological treatment options for osteoporosis include the use of antiresorptive therapies, such as bisphosphonates (e.g. alendronate, ibandronate, risedronate, zoledronic acid), calcitonin, RANKL-inhibitors (e.g., denosumab), strontium ranelate, and selective estrogen modulators (e.g. raloxifene), as well as anabolic intermittent parathyroid hormone (teriparatide). Ongoing pre-clinical and clinical trials are currently examining anti-resorptive cathepsin-K inhibitors (e.g., odanacatib), and anabolic Wnt-pathway inhibitors (e.g., sclerostin, dickkopf-1) [5] for their efficacy in postmenopausal osteoporotic patients. More detailed information about the mechanisms of action for these emerging therapeutics can be found in a companion paper in this journal by Ng and Martin.

The goal of this review paper is to briefly summarize the biomechanical basis of current treatment strategies and to define how understanding the different biomechanical mechanisms leading to reduced fracture resistance may help identify new targets for pharmacological treatments that allow physicians to treat locally (i.e., personally) to reduce fracture incidence globally.

A paradigm shift

Currently, most people have to lose significant bone mass (i.e., essentially become osteopenic or osteoporotic) before being diagnosed and treated for osteoporosis. This is problematic, because a person can lose as much 33% of their bone strength between 45 and 65 years of age before treatments typically begin [6]. Bone strength recovers 0-5% in 18 months following treatment [7], which is largely limited to rebuilding lost bone. Although fracture rate has stabilized [8], the current strategy is not optimal because it leads to a loss in strength that unnecessarily increases fracture risk before treatment. Prevention strategies are an important investment for improving healthcare. For example, most people no longer have to suffer a heart attack before being diagnosed and treated for heart disease [9]. Although we are moving in this direction, we have a long way to go before we can say the same about fragility fractures. A prevention strategy would be difficult to implement for bone presently for many reasons. Critically, we lack crucial information about inter-individual differences in skeletal aging that limits existing technologies from accurately predicting a person's future bone strength before loss of bone mass, organization, or material quality occurs.

A key factor in breaking through the traditional paradigm is to shift the scientific perspective ever so slightly and to embrace a very simple concept: *people age differently*. Individuals arrive at reduced fracture resistance through biomechanical pathways that are biologically distinct. As shown in Figure 3, reduced fracture resistance with aging may arise from many biomechanical pathways, such as having genetically slender bones [10,11], excessive resorption [12], impaired periosteal expansion [13], or reduced tissue-toughness arising from increased collagen cross-linking [14]. Each of these well recognized biomechanical pathways lead to reduced fracture resistance through different biological mechanisms, each of which may require different treatment strategies. Recognizing these different biomechanical pathways provides an opportunity to devise treatment strategies that best improve bone strength based on the biomechanical and biological needs of the individual. Thus, better understanding inter-individual differences in how people age will be a critical factor driving the development of advanced diagnostic technologies that facilitate personalized pharmacological treatment approaches.

Biomechanical mechanisms for personalized prevention of bone fracture

Biomechanical mechanisms responsible for fracture susceptibility can be defined at multiple levels of hierarchy. There is a significant body of research devoted to understanding the individual components of each of these foundations upon which the basis for fracture susceptibility is built. Despite this underlying knowledge, the current state of the art in diagnostics is limited to factors that reflect, but may not be directly indicative of fracture risk.

DEXA

Clinically, bone mass is most commonly assessed by dual-energy X-ray absorptiometry (DEXA). DEXA uses radiographic techniques to quantify the average attenuation of X-rays across a defined planar area [15]. The patient's areal bone mineral density (aBMD) is compared to a standard reference population (female Caucasians aged 20-29 years old) to derive a T-score, representing the patient's individual aBMD in relation to standard deviations from the reference population mean [15]. The risk of fracture approximately doubles for every standard deviation decrease in BMD versus the reference population [16-18]. Guidelines for osteoporosis diagnosis have been established by the World Health Organization by characterizing T-scores less than -2.5 as osteoporotic, or severely osteoporotic when combined with an existing fragility fracture [1,15]. Patients with T-scores between -1 to -2.5 are described as osteopenic, and represent individuals with a wide range of fracture risk [19,20]. Although bone loss can occur at different sites and at different rates, hip fracture is the most severe complication of osteoporosis and can be used to predict future fracture risk at all other sites [21], including vertebral, intertrochanteric, proximal humerus and wrist - the most common sites for fragility fractures [5]. Therefore, measurement of aBMD of the proximal femur has been most frequently used to predict fractures, whereas a measurement of aBMD in the lumbar spine is most often used for monitoring efficacy of therapeutic intervention [15]. DEXA is a fairly inexpensive technique with low radiation exposure, but requires a skilled operator for proper positioning of the patient [22], and depending on the anatomic site, is subject to artifacts such as spondylosis or vertebral

compression fractures which may over-estimate the local aBMD [23,24]. Additionally, since DEXA utilizes an areal measurement for normalization, the size of the bone may affect its apparent density [25], and internal geometric factors may bias the results [5].

FRAX

The risk of bone fracture is high when osteoporosis is present. However, the risk of fracture is not negligible when BMD is normal, and other clinical factors can be used to enhance the predictability of the technique [21]. The Fracture Resistance Assessment Tool (FRAX), is the most common fracture risk calculator, and uses clinically accessible risk factors to estimate a patient's 10 year fracture probability [21,26]. Nine additional factors (age, body mass index, parental history of hip fracture, exposure of systemic glucocorticoids, past fragility fracture, smoking status, high alcohol intake, and presence of rheumatoid arthritis, other causes of secondary osteoporosis) can be combined with or without BMD to provide additive assessment of fracture risk [26]. These nine factors were readily available in large database studies, and are associated with fracture risks that are greater than when BMD changes alone could predict [26].

Biochemical Markers

The intention of FRAX is to provide a platform upon which to add new validated risk indicators as they become available to the scientific community [27]. Bone formation and resorption is a dynamic process, and multiple metabolic states can present the same bone mineral density with widely different pathologic significance [28]. Biochemical indicators of bone formation and resorption have been proposed to augment BMD to provide dynamic indicators of skeletal activity, but cannot reliably be used to estimate BMD levels or predict or diagnose osteoporosis [29]. Whereas a long-term observational period is required to monitor BMD in response to disease or therapy, biochemical markers may be effective at assessing bone metabolism at the time of measurement, and can be used to monitor progression of the disease, assess the treatment effect of a drug, or assess adherence to drug therapy [30]. Despite these advantages, biochemical markers have not been incorporated into assessment tools such as FRAX due to their high variability and lack of availability of this common data across large populations, preventing the establishment of specific reference standards to provide normative population data on which to base a treatment or diagnosis [30,31].

Engineering theories, FEA, Statistical Shape Modeling, and Active Shape Modeling

Fragility fractures occur at both diaphyseal and metaphyseal sites. The strength of diaphyseal bone is readily predicted from engineering beam theory since these structures tend to resemble a hollow cylinder [32]. However, the strength of more complex cortico-cancellous structures cannot be readily predicted with certainty from beam theory. Thus, we must rely on methods like finite element analysis (FEA) [33,34] or statistical shape and density modeling [35] to estimate bone strength. These methods predict strength after incorporating details of an individual's actual morphology and tissue density. These methods provide far greater sensitivity to the changes in strength that occur with aging compared to BMD [6], but at increased computational costs. One of the challenges for engineering-based methods is that fracture resistance does not reflect a single mechanical

property (i.e., strength), but actually represents a repertoire of properties including strength, toughness, fatigability, and brittleness. The failure and fatigue properties of bone are more difficult to estimate from engineering analyses because they involve nonlinear material behaviors that are computationally difficult to incorporate into models. Nevertheless, much progress is being made in this area [36,37]. An emerging area of research is the use of Active Shape Modeling to not only predict fracture risk as well as BMD, but to also provide critical insight into morphological features that differ between fracture and non-fracture groups [38]. Variation in bone morphology, density, and density distribution together provide important insight into the underlying biological factors contributing to fracture risk and provide clues as to how therapies may be strategically targeted to improve bone strength. Importantly, Active Shape Modeling also reveals how geometrical and density measures covary [38]. The covariation among bone traits can be related back to the functional adaptation process [39,40], thereby providing insight into adaptive features of the aging skeleton that can be strategically enhanced using prophylactic treatments. Technologies such as Active Shape Modeling [38] and statistical shape and density modeling [35] may also provide feedback to the clinicians to ensure that the treatment had the intended effect regarding the location and magnitude of bone loss and gain. This critical feedback cannot be obtained presently with BMD.

Biomechanical mechanisms help explain differential aging

The irony of medicine is that physicians treat the *individual* based on biological principals that were derived from an analysis of how the *population average* of certain traits change over time [41]. A critical question to ask is whether osteoporosis is a one-size-fits-all disease. Mounting evidence supports the idea that individuals grow in different ways [42,43] and age in different ways [44-46]. The inter-individual differences in growth and aging are sufficiently large to be clinically meaningful. For example, slender bones are at increased risk of fracturing throughout life due to their narrow diameter and potential accumulation of microdamage given the naturally suppressed intracortical remodeling [10,13,39,40,47]. In contrast, robust bones potentially become more fragile with age as increasing porosities coalesce and cortical area progressively decreases from continuous endosteal remodeling [46,48]. Further, men and women show different age-related changes in trabecular architecture [49]. This sex-specific effect is important as bone loss due to age-changes in trabecular connectivity (women) has a more deleterious effect mechanically compared to bone loss resulting from age-changes in trabecular thickness (men) [50]. Additionally, in some circumstances, bone loss may play a secondary role to trabecular architectural changes that may predispose an individual to fracture [51]. These different biomechanical pathways leading to reduced fracture resistance provide important insight into prophylactic strategies that can maintain or increase strength more strategically by targeting specific biological processes [52]. These and other studies clearly indicate that more research is needed to better connect molecular mechanisms with biomechanical mechanisms to better understand inter-individual differences in skeletal aging.

As described, BMD measures are the gold standard for clinically assessing fracture risk [53]. This measure has proven useful in the prediction of an individual's bone strength in relation to the population average, and FRAX, and biochemical measures have sought to augment its

predictive power. However, these assessment tools fail to provide clinicians with a detailed assessment of the morphological structure, mechanical properties, and tissue quality of bone and their interactions [6,54-57] needed to define why a person is at increased risk of fracturing. Important traits that influence this variation in strength include the outer and inner diameters of the bony cortex, the degree to which the cortical matrix is mineralized, and the pore volume present in the cortex attributable to remodeling; all of these factors are inadequately accounted for in BMD values [58-63]. However, much progress has been made in using the image generated during the DEXA scan to derive morphological features of bone that can be related to bone strength [64]. Other traditional techniques, such as CT [33,65] and radiographs [4], as well as emerging diagnostic tools including Raman spectroscopy [66,67] or microindentation [68] may continue to improve our ability to discern these complex parameters associated with fracture resistance.

Two key factors to consider going forward

There are two key factors that may benefit efforts aimed at using pharmacological treatments in a more biomechanically strategic manner - time (when to treat) and location (what tissue to target).

Time

Deciding at what age to best treat an individual is perhaps one of the greatest challenges for advancing our understanding of how to use osteoporotic treatments most effectively. Currently, treating individuals after 65 years of age attempts to re-build lost bone, which has been somewhat effective but is certainly not optimal as a long-term treatment strategy because this requires an individual to lose strength before they can be treated. Ideally, we want to maintain strength with aging. This means we need to slow bone loss before it begins and promote periosteal expansion to mechanically offset the inevitable bone loss [2,52,69]. A challenge here is that most people enter the aging process in a generally healthy state; as such, it is certainly reasonable to ask, why should we treat healthy individuals? However, like heart disease, small pieces of information collected over time provide the physician with critical information to know when a person is heading toward an unhealthy state [9]. Research examining longitudinal databases to identify patterns in the way people age could provide new insight into key factors that predict differential aging and that may identify critical ages in which treatments may be more effective.

Location

Treating bone for osteoporosis is like buying a house. Everyone knows that when buying a home, the three things that matter most are location, location, location. The same holds for bone. The location of the biological target matters greatly, because the skeleton undergoes many changes with aging (Figure 1) and the degree to which each of these factors change with aging varies among individuals. For structures subjected to bending or torsional loads, bone strength is proportional to the 3rd power of bone width. This means that the greatest effect from a pharmacological standpoint may be to increase bone strength by targeting periosteal expansion using an anabolic treatment (e.g., teriparatide, Wnt-pathway inhibitors) [52,70]. However, this simple strategy may not be universal. Patients that tend to have

slender bones may benefit from an anabolic treatment (e.g., teriparatide, Wnt-pathway inhibitors), focused on increasing periosteal apposition to offset the inevitable endocortical bone loss while increasing their mechanical strength [39]. In contrast, patients that have robust bones already have the external size to be strong but they may show greater bone loss with aging [46], suggesting that these structures would benefit from slowing bone loss (e.g., bisphosphonates, denosumab). We also know that age-related changes in tissue-level mechanical properties play a critical role in fragility as they can severely reduce fracture resistance independent of changes in bone mass [14]. Thus, treatments that reduce age-related increases in cross-linking may benefit those with altered matrix and reduced toughness. There are tremendous opportunities to target factors like matrix mineralization, collagen cross-linking, and water to improve fracture resistance [55,71,72].

Conclusion

Evidence is mounting that people age differently. The number of treatment options currently on the market and in the pipeline is growing. Our ability to fully utilize these treatments in biomechanically strategic manners is lagging. This gap will be solved by increasing the number of collaborations among scientists in the pharmaceutical industry, endocrinology, orthopaedics, cell/molecular biology, and bioengineering. Identifying novel molecular mechanisms is clearly important for developing new treatment options. However, this effort only addresses one part of the solution. There must also be consideration of the specific biomechanical mechanisms defining how these molecular pathways ultimately impact whole bone fracture resistance. Thus, better understanding how molecular mechanisms relate to biomechanical mechanisms will benefit efforts to use the growing number of pharmacological treatments to reduce fracture incidence more strategically, more effectively, and more economically.

Acknowledgments

Research reported in this publication was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Numbers AR44927 and AR062522. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Kanis J. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet*. 2002; 359:1929–1936. [PubMed: 12057569]
2. Albright F, Smith PH, Richardson AM. Post-menopausal osteoporosis. Its clinical features. *JAMA*. 1941; 116:2465–2474.
3. Smith RW, Walker RR. Femoral expansion in aging women: Implications for osteoporosis and fractures. *Science*. 1964; 145:156–157. [PubMed: 14171549]
4. Singh M, Nagrath AR, Maini PS. Changes in trabecular pattern of the upper end of the femur as an index of osteoporosis. *J Bone Joint Surg Am*. 1970; 52:457–467. [PubMed: 5425640]
5. Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. *Lancet*. 2011; 377:1276–1287. [PubMed: 21450337]
6. Keaveny TM, Kopperdahl DL, Melton LJ 3rd, Hoffmann PF, Amin S, Riggs BL, Khosla S. Age-dependence of femoral strength in white women and men. *J Bone Miner Res*. 2010; 25:994–1001. [PubMed: 19874201]

7. Keaveny TM, McClung MR, Wan X, Kopperdahl DL, Mitlak BH, Krohn K. Femoral strength in osteoporotic women treated with teriparatide or alendronate. *Bone*. 2012; 50:165–170. [PubMed: 22015818]
8. Cooper C, Cole ZA, Holroyd CR, Earl SC, Harvey NC, Dennison EM, Melton LJ, Cummings SR, Kanis JA. Secular trends in the incidence of hip and other osteoporotic fractures. *Osteoporos Int*. 2011; 22:1277–1288. [PubMed: 21461721]
9. Gielen S, Landmesser U. The Year in Cardiology 2013: cardiovascular disease prevention. *Eur Heart J*. 2014
10. Milgrom C, Giladi M, Simkin A, Rand N, Kedem R, Kashtan H, Stein M, Gomori M. The area moment of inertia of the tibia: a risk factor for stress fractures. *J Biomech*. 1989; 22:1243–1248. [PubMed: 2625424]
11. Darling AL, Hakim OA, Horton K, Gibbs MA, Cui L, Berry JL, Lanham-New SA, Hart KH. Adaptations in tibial cortical thickness and total volumetric bone density in postmenopausal South Asian women with small bone size. *Bone*. 2013; 55:36–43. [PubMed: 23531785]
12. Parfitt AM. Age-related structural changes in trabecular and cortical bone: cellular mechanisms and biomechanical consequences. *Calcified Tissue International*. 1984; 36:S123–128. [PubMed: 6430512]
13. Szulc P, Seeman E, Duboeuf F, Sornay-Rendu E, Delmas PD. Bone fragility: failure of periosteal apposition to compensate for increased endocortical resorption in postmenopausal women. *J Bone Miner Res*. 2006; 21:1856–1863. [PubMed: 17002580]
14. Farr JN, Drake MT, Amin S, Melton LJ 3rd, McCready LK, Khosla S. In Vivo assessment of bone quality in postmenopausal women with type 2 diabetes. *J Bone Miner Res*. 2013
15. Eastell R. Identification and management of osteoporosis in older adults. *Medicine*. 2013; 41:47–52. •• This review is a good reference for current methodologies in identifying osteoporosis and the pharmaceuticals currently available to clinicians, with notes on their efficacy.
16. Melton LJ 3rd, Atkinson EJ, O'Fallon WM, Wahner HW, Riggs BL. Long-term fracture prediction by bone mineral assessed at different skeletal sites. *J Bone Miner Res*. 1993; 8:1227–1233. [PubMed: 8256660]
17. Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, Genant HK, Palermo L, Scott J, Vogt TM. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. *Lancet*. 1993; 341:72–75. [PubMed: 8093403]
18. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *Bmj*. 1996; 312:1254–1259. [PubMed: 8634613]
19. Watts NB. Fundamentals and pitfalls of bone densitometry using dual-energy X-ray absorptiometry (DXA). *Osteoporos Int*. 2004; 15:847–854. [PubMed: 15322740]
20. Yu EW, Finkelstein JS. Bone density screening intervals for osteoporosis: one size does not fit all. *JAMA*. 2012; 307:2591–2592. [PubMed: 22735425]
21. McCloskey E, Johansson H, Oden A, Kanis JA. Fracture risk assessment. *Clin Biochem*. 2012; 45:887–893. •• This review is a good reference for current methodologies in identifying osteoporosis and the pharmaceuticals currently available to clinicians, with notes on their efficacy. [PubMed: 22579965]
22. Guglilmi G, Diano D, Ponti F, Bazzocchi A. Quality assurance in bone densitometry. *Curr Radiol Rep*. 2014; 2:33.
23. Eastell R. Treatment of postmenopausal osteoporosis. *N Engl J Med*. 1998; 338:736–746. [PubMed: 9494151]
24. Perilli E, Briggs AM, Kantor S, Codrington J, Wark JD, Parkinson IH, Fazzalari NL. Failure strength of human vertebrae: prediction using bone mineral density measured by DXA and bone volume by micro-CT. *Bone*. 2012; 50:1416–1425. [PubMed: 22430313]
25. Leslie WD. Clinical review: Ethnic differences in bone mass--clinical implications. *J Clin Endocrinol Metab*. 2012; 97:4329–4340. • This review highlights the differences in bone mineral density between geographic and ethnic groups that may explain previously reported fracture rate differences between populations and should be considered when clinically assessing fracture risk. [PubMed: 23055542]

26. Kanis JA, McCloskey E, Johansson H, Oden A, Leslie WD. FRAX((R)) with and without bone mineral density. *Calcif Tissue Int.* 2012; 90:1–13. [PubMed: 22057815]
27. Kanis JA, Oden A, Johansson H, Borgstrom F, Strom O, McCloskey E. FRAX and its applications to clinical practice. *Bone.* 2009; 44:734–743. [PubMed: 19195497]
28. Nishizawa Y, Ohta H, Miura M, Inaba M, Ichimura S, Shiraki M, Takada J, Chaki O, Hagino H, Fujiwara S, et al. Guidelines for the use of bone metabolic markers in the diagnosis and treatment of osteoporosis (2012 edition). *J Bone Miner Metab.* 2013; 31:1–15. [PubMed: 23143508]
29. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J, Committee of Scientific Advisors of the International Osteoporosis F. The use of biochemical markers of bone turnover in osteoporosis. Committee of Scientific Advisors of the International Osteoporosis Foundation. *Osteoporos Int.* 2000; 11(Suppl 6):S2–17. [PubMed: 11193237]
30. Brown JP, Albert C, Nassar BA, Adachi JD, Cole D, Davison KS, Dooley KC, Don-Wauchope A, Douville P, Hanley DA, et al. Bone turnover markers in the management of postmenopausal osteoporosis. *Clin Biochem.* 2009; 42:929–942. [PubMed: 19362543]
31. Vasikaran S, Eastell R, Bruyere O, Foldes AJ, Garnero P, Griesmacher A, McClung M, Morris HA, Silverman S, Trenti T, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int.* 2011; 22:391–420. [PubMed: 21184054]
32. van der Meulen MC, Jepsen KJ, Mikic B. Understanding bone strength: size isn't everything. *Bone.* 2001; 29:101–104. [PubMed: 11502469]
33. Keyak JH, Rossi SA, Jones KA, Skinner HB. Prediction of femoral fracture load using automated finite element modeling. *J Biomech.* 1998; 31:125–133. [PubMed: 9593205]
34. Crawford RP, Cann CE, Keaveny TM. Finite element models predict in vitro vertebral body compressive strength better than quantitative computed tomography. *Bone.* 2003; 33:744–750. [PubMed: 14555280]
35. Bredbenner TL, Eliason TD, Potter RS, Mason RL, Havill LM, Nicoletta DP. Statistical shape modeling describes variation in tibia and femur surface geometry between control and incidence groups from the osteoarthritis initiative database. *J Biomech.* 2010; 18:1780–1786. [PubMed: 20227696]
36. Gong H, Zhang M, Fan Y, Kwok WL, Leung PC. Relationships between femoral strength evaluated by nonlinear finite element analysis and BMD, material distribution and geometric morphology. *Ann Biomed Eng.* 2012; 40:1575–1585. •• The authors quantify proximal femur strength using bone mineral density, quantitative computed tomography, and finite element analysis to account for both morphological and compositional factors of bone strength. [PubMed: 22258889]
37. Keaveny TM, Hoffmann PF, Singh M, Palermo L, Bilezikian JP, Greenspan SL, Black DM. Femoral bone strength and its relation to cortical and trabecular changes after treatment with PTH, alendronate, and their combination as assessed by finite element analysis of quantitative CT scans. *J Bone Miner Res.* 2008; 23:1974–1982. [PubMed: 18684084]
38. Goodyear SR, Barr RJ, McCloskey E, Alesci S, Aspden RM, Reid DM, Gregory JS. Can we improve the prediction of hip fracture by assessing bone structure using shape and appearance modelling? *Bone.* 2013; 53:188–193. [PubMed: 23220597]
39. Jepsen KJ, Centi A, Duarte GF, Galloway K, Goldman H, Hampson N, Lappe JM, Cullen DM, Greeves J, Izard R, et al. Biological constraints that limit compensation of a common skeletal trait variant lead to inequivalence of tibial function among healthy young adults. *J Bone Miner Res.* 2011; 26:2872–2875. [PubMed: 21898595]
40. Jepsen KJ, Evans R, Negus C, Gagnier JJ, Centi A, Erlich T, Hadid A, Yanovich R, Moran DS. Variation in tibial functionality and fracture susceptibility among healthy, young adults arises from the acquisition of biologically distinct sets of traits. *J Bone Miner Res.* 2013; 28:1290–1300. [PubMed: 23362125]
41. Seeman E. The growth and age-related origins of bone fragility in men. *Calcif Tissue Int.* 2004; 75:100–109. [PubMed: 15383923]
42. Pandey N, Bhola S, Goldstone A, Chen F, Chrzanowski J, Terranova CJ, Ghillani R, Jepsen KJ. Inter-individual variation in functionally adapted trait sets is established during post-natal growth

- and predictable based on bone robusticity. *J Bone Miner Res.* 2009; 24:1969–1980. [PubMed: 20001599]
43. Bhola S, Chen J, Fusco J, Duarte GF, Andarawis-Puri N, Ghillani R, Jepsen KJ. Variation in childhood skeletal robustness is an important determinant of cortical area in young adults. *Bone.* 2011; 49:799–809. [PubMed: 21810492]
 44. Christiansen BA, Kopperdahl DL, Kiel DP, Keaveny TM, Bouxsein ML. Mechanical contributions of the cortical and trabecular compartments contribute to differences in age-related changes in vertebral body strength in men and women assessed by QCT-based finite element analysis. *J Bone Miner Res.* 2011; 26:974–983. [PubMed: 21542000]
 45. Jepsen KJ, Andarawis-Puri N. The amount of periosteal apposition required to maintain bone strength during aging depends on adult bone morphology and tissue-modulus degradation rate. *J Bone Miner Res.* 2012; 27:1916–1926. [PubMed: 22532507]
 46. Epelboym Y, Gendron RN, Mayer J, Fusco J, Nasser P, Gross G, Ghillani R, Jepsen KJ. The inter-individual variation in femoral neck width is associated with the acquisition of predictable sets of morphological and tissue-quality traits and differential bone loss patterns. *J Bone Miner Res.* 2012; 27:1501–1510. [PubMed: 22461103]
 47. Crossley K, Bennell KL, Wrigley T, Oakes BW. Ground reaction forces, bone characteristics, and tibial stress fracture in male runners. *Med Sci Sports Exerc.* 1999; 31:1088–1093. [PubMed: 10449008]
 48. Bell KL, Loveridge N, Reeve J, Thomas CD, Feik SA, Clement JG. Super-osteons (remodeling clusters) in the cortex of the femoral shaft: influence of age and gender. *Anat Rec.* 2001; 264:378–386. [PubMed: 11745093]
 49. Amin S, Khosla S. Sex- and age-related differences in bone microarchitecture in men relative to women assessed by high-resolution peripheral quantitative computed tomography. *J Osteoporos.* 2012; 2012:129760. •• The authors review the body of literature wherein high-resolution peripheral quantitative computed tomography was used to quantify trabecular and cortical differences in males relative to females, highlighting factors that may in part explain differences in fracture risk between sexual cohorts. [PubMed: 22496983]
 50. Silva MJ, Gibson LJ. Modeling the mechanical behavior of vertebral trabecular bone: effects of age-related changes in microstructure. *Bone.* 1997; 21:191–199. [PubMed: 9267695]
 51. Ciarelli TE, Fyhrie DP, Schaffler MB, Goldstein SA. Variations in three-dimensional cancellous bone architecture of the proximal femur in female hip fractures and in controls. *J Bone Miner Res.* 2000; 15:32–40. [PubMed: 10646112]
 52. Seeman E. Periosteal bone formation--a neglected determinant of bone strength. *N Engl J Med.* 2003; 349:320–323. [PubMed: 12878736]
 53. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D. Guidelines for diagnosis and management of osteoporosis. The European Foundation for Osteoporosis and Bone Disease. *Osteoporos Int.* 1997; 7:390–406. [PubMed: 9373575]
 54. Bouxsein ML, Parker RA, Greenspan SL. Forearm bone mineral densitometry cannot be used to monitor response to alendronate therapy in postmenopausal women. *Osteoporos Int.* 1999; 10:505–509. [PubMed: 10663352]
 55. Vashishth D. The role of the collagen matrix in skeletal fragility. *Curr Osteoporos Rep.* 2007; 5:62–66. [PubMed: 17521507]
 56. Tommasini SM, Nasser P, Hu B, Jepsen KJ. Biological Co-adaptation of Morphological and Composition Traits Contributes to Mechanical Functionality and Skeletal Fragility. *J Bone Miner Res.* 2008; 23:236–246. [PubMed: 17922614]
 57. Schlecht SH, Jepsen KJ. Functional integration of skeletal traits: an intraskeletal assessment of bone size, mineralization, and volume covariance. *Bone.* 2013; 56:127–138. • The authors highlight the natural variation in morphological and compositional skeletal traits that partially define bone strength across a population, highlighting the need to consider more factors than just bone mineral density scores when clinically assessing bone fragility. [PubMed: 23721816]
 58. Boutroy S, Hans D, Sornay-Rendu E, Vilaythiou N, Winzenrieth R, Chapurlat R. Trabecular bone score improves fracture risk prediction in non-osteoporotic women: the OFELY study. *Osteoporos Int.* 2013; 24:77–85. [PubMed: 23070481]

59. Djonic D, Milovanovic P, Nikolic S, Ivovic M, Marinkovic J, Beck T, Djuric M. Inter-sex differences in structural properties of aging femora: implications on differential bone fragility: a cadaver study. *J Bone Miner Metab.* 2011; 29:449–457. [PubMed: 21127922]
60. Donnelly E. Methods for assessing bone quality: a review. *Clin Orthop Relat Res.* 2011; 469:2128–2138. [PubMed: 21116752]
61. Kalpakcioglu BB, Engelke K, Genant HK. Advanced imaging assessment of bone fragility in glucocorticoid-induced osteoporosis. *Bone.* 2011; 48:1221–1231. [PubMed: 21320651]
62. Kolta S, Paratte S, Amphoux T, Persohn S, Campana S, Skalli W, Paternotte S, Argenson JN, Bouler JM, Gagey O, et al. Bone texture analysis of human femurs using a new device (BMA) improves failure load prediction. *Osteoporos Int.* 2012; 23:1311–1316. [PubMed: 21656265]
63. Li GW, Chang SX, Xu Z, Chen Y, Bao H, Shi X. Prediction of hip osteoporotic fractures from composite indices of femoral neck strength. *Skeletal Radiol.* 2013; 42:195–201. [PubMed: 22714125]
64. Danielson ME, Beck TJ, Karlamangla AS, Greendale GA, Atkinson EJ, Lian Y, Khaled AS, Keaveny TM, Kopperdahl D, Ruppert K, et al. A comparison of DXA and CT based methods for estimating the strength of the femoral neck in post-menopausal women. *Osteoporos Int.* 2013; 24:1379–1388. [PubMed: 22810918]
65. Zebaze RM, Ghasem-Zadeh A, Bohte A, Iuliano-Burns S, Mirams M, Price RI, Mackie EJ, Seeman E. Intracortical remodelling and porosity in the distal radius and post mortem femurs of women: a cross-sectional study. *Lancet.* 2010; 375:1729–1736. [PubMed: 20472174]
66. Ookagbare PI, Morris MD. Fluorocarbon fiber-optic Raman probe for non-invasive Raman spectroscopy. *Appl Spectrosc.* 2012; 66:728–730. [PubMed: 22732546]
67. Ookagbare PI, Morris MD. Polymer-capped fiber-optic Raman probe for non-invasive Raman spectroscopy. *Analyst.* 2012; 137:77–81. [PubMed: 22059232]
68. Bridges D, Randall C, Hansma PK. A new device for performing reference point indentation without a reference probe. *Rev Sci Instrum.* 2012; 83:044301. [PubMed: 22559552]
69. Seeman E. The periosteum--a surface for all seasons. *Osteoporos Int.* 2007; 18:123–128. [PubMed: 17180552]
70. Allen MR, Hock JM, Burr DB. Periosteum: biology, regulation, and response to osteoporosis therapies. *Bone.* 2004; 35:1003–1012. [PubMed: 15542024]
71. Boskey AL, Coleman R. Aging and bone. *J Dent Res.* 2010; 89:1333–1348. [PubMed: 20924069]
72. Gallant MA, Brown DM, Hammond M, Wallace JM, Du J, Deymier-Black AC, Almer JD, Stock SR, Allen MR, Burr DB. Bone cell-independent benefits of raloxifene on the skeleton: A novel mechanism for improving bone material properties. *Bone.* 2014 •• The authors present data from a novel experiment on both canine and human bone devoid of living cells, highlighting the ability of raloxifene to improve intrinsic bone toughness by increasing matrix hydration and energy absorption.

Highlights

- The number of treatment options on the market and in the pipeline is growing.
- Ability to use these treatments in biomechanically strategic manners is lagging.
- Reduced fracture resistance arises through different biomechanical pathways.
- People aging differently and need to be treated more strategically.

Figure 1.

Sagittal section of a human proximal femur (25 micron voxel size; nanotom-s, phoenix|x-ray, GE Measurement & Control; Wunstorf, Germany) showing the many changes in structure and tissue-level mechanical properties that occur with aging. Potential biomarkers for each pathway are shown in parentheses.

Figure 2.

The number of available pharmacological treatment options and those in the pipeline has steadily increased over the last two decades. Examples of antiresorptive and anabolic treatments are shown in the medicine chests.

Figure 3.

Reduced fracture resistance can arise through multiple biomechanical pathways that are biologically distinct and that may require different strategies for pharmacological treatment to best improve bone fracture resistance.