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ORIGINAL ARTICLE

Bone quality: where do we go from here?

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Abstract As was true 10 years ago, tremendous interest surrounds the concept of ''bone quality,'' as shown by the intense and growing research activity in the field. The urgency to advance knowledge in this area is motivated by the need to understand not only the causes of increased skeletal fragility with aging and disease, but also the mechanisms by which drugs reduce fracture risk. As reflected in the preceding articles, in the past decade collaborations between biologists, physicists, engineers and clinicians have led to new insights regarding the biological, material and structural features that contribute to skeletal fragility. Despite these new insights, important issues remain unresolved. Our challenges lie in identifying, describing and understanding the totality of features and characteristics that determine a bone's ability to resist fracture, and using this information to identify new therapeutic targets and develop better biomarkers and noninvasive imaging modalities. This summary is intended to integrate reports in the literature with presentations and discussions that occurred during the meeting, to highlight areas of consensus and those of continued controversy, and thus to identify critical areas for future research.

Quality

According to *The Free On-line Dictionary of Computing* (1993–2003, Denis Howe), quality is the totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs, not to be mistaken for ''degree of excellence'' or ''fitness for use,'' which meet only part of the definition.

What is bone quality?

As previously mentioned, the term ''bone quality'' has been widely used to explain a number of clinical observations that cannot be readily explained by bone mineral density (BMD) measurements. Defining bone quality as that which is not explained by BMD suffers greatly from the fact that the definition is dependent on the limitations of a clinical technique and, therefore, would change if a new (i.e., better) measurement technique was introduced. Moreover, this approach to defining bone quality is not grounded in physical or biomechanical principles.

Considering the definition of *quality* stated above, it is reasonable to consider that the ability of a bone to resist fracture is among the most, if not the most, important of its ''stated or implied needs.'' The skeleton has many functions, including allowing for locomotion, protection of vital internal organs and assisting in mineral homeostasis and hematopoesis. However, if a bone is broken, it can fulfill few, if any, of its many functions. Individuals who suffer a fracture are special. They may be more likely to trip or fall, but they are also liable to have skeletal features that distinguish them from individuals who fall but do not fracture. Low BMD is part of the explanation, but alterations in other skeletal traits also contribute to increased fracture risk. Although a consensus definition of bone quality remains elusive, an operational definition of bone quality is proposed to be the ''totality of features and characteristics that influence a bone's ability to resist fracture.''

Our challenges lie in identifying, describing and understanding the totality of features and characteristics that determine a bone's ability to resist fracture, and using this information to identify novel therapeutic targets and develop new biomarkers and noninvasive imaging modalities with improved clinical utility.

Why do bones break? Expanding the view of bone strength

We do not fully understand the answer to this deceptively straightforward question. Fractures result from a catastrophic structural failure of the whole bone that is initiated at the material level. For simple objects made up of a uniform material, the object breaks (i.e., fails)

when the load applied to the object generates an internal stress that exceeds the strength of the material [1, 2]. However, as Dr. Jepsen pointed out, bone is a geometrically complex, composite material characterized by an elaborate array of mechanical properties [2]. As such, there is no single property that is adequate to describe "bone strength." Which biomechanical properties or combination thereof—that is, the ability to resist deformation (elastic modulus or stiffness), to absorb energy (toughness), to accommodate repetitive loading (fatigue strength), or to inhibit the progression of a crack (fracture toughness)—are most important for a bone's resistance to fracture remain to be elucidated.

Many of the speakers reviewed the concept that the mechanical behavior of a whole bone depends on the morphology of the bone (i.e., both the amount and distribution of bone material), as well as the intrinsic properties of bone material itself. Broadly, therefore, the factors most likely to influence the resistance to fracture include: (1) the overall composition (i.e., proportion of mineral, collagen, water and matrix proteins); (2) the physical and biochemical characteristics of these components (i.e., nature of the collagen, degree and type of collagen cross-linking, size and structure of hydroxyapatite crystals and degree of mineralization); (3) the morphology and architecture (i.e., bone size, cortical cross-sectional geometry, porosity, osteon size and density and trabecular microarchitecture); and (4) the amount and nature of preexisting microdamage (i.e., crack length, density and location).

Bones may break because they are too flexible, too weak, do not absorb enough energy and/or are not resistant to repetitive loading [3]. The characteristics that enhance a bone's ability to resist fracture in 1 of these conditions may actually be detrimental in another. For example, reducing the rate of bone turnover leads to an increase in the average degree of mineralization of the bone tissue [4], a feature that has been associated with increased elastic modulus (stiffness), but decreased toughness, particularly during impact loading [5, 6]. Bisphosphonate treatment reduces bone turnover, increases the mean degree of mineralization [7, 8] and reduces fracture risk [9]. In comparison, intermittent administration of parathyroid hormone (PTH) increases bone turnover, reduces the mean degree of mineralization [10] and yet also reduces fracture risk [11]. Other material and structural properties besides mineralization are likely affected by these therapies. Because skeletal fragility is determined by the integration of these properties, looking at 1 feature in isolation can be misleading. Nonetheless, this simple example underscores the need to identify the relative role of different bone morphologic and material traits in determining skeletal fragility. Understanding the relative balance of these determinants of bone quality may be critical for optimizing therapies.

To understand why bones fracture, it is not enough to know the biomechanical properties of bone. It is also critical to combine this information with knowledge of how the bone is loaded during situations that produce fractures. For example, for fractures associated with impact loading conditions, such as those experienced during a fall, characteristics that influence the ability of bone to absorb energy or to resist the propagation of cracks may play the dominant role in determining fracture risk. In contrast, for fractures associated with repetitive loads of low magnitude, characteristics that influence the ability of bone to resist the accumulation of fatigue-related damage may predominate.

Participants at the symposium agreed that to tease out the relative contributions to bone quality, experimental investigations of the biomechanical properties of bone should be expanded to include not only traditional mechanical testing approaches, but also cyclic loading of whole bones and fracture mechanics approaches. In addition, mathematical modeling efforts, such as finite element analysis, should be exploited to systematically vary different bone characteristics while maintaining others constant to estimate the respective relative impact of each on bone strength [12, 13]. Research combining these testing approaches with assessments of the array of bone material and morphologic traits will help to clarify why bones break, and therefore identify what features of bone quality are most important for preventing fractures.

In summary, the mechanical behavior of a bone, and whether it will break under a given loading condition, is governed by the interaction between the properties of the bone material and how this material is arranged spatially. The concept of a single "bone strength" must be expanded to include the entire repertoire of biomechanical properties. Additional research is needed to determine which failure mechanism (or combination thereof) governs fragility fractures, and to better understand why bones break.

The impact of cellular, organic, and inorganic composition on bone quality

Bone has been viewed as a composite material with 2 primary constituents: mineral and collagen. Dr. Currey reviewed the notion that in structurally normal bone, the mineral provides stiffness and strength, whereas collagen affords ductility and toughness [1]. However, the specific interaction between mineral and collagen is poorly understood. Moreover, the precise characteristics of the mineral and collagen that confer to each its characteristic behavior are also not completely understood [1, 14, 15]. For instance, Dr. Boskey reported that increased mineral crystal size can have positive, negative or negligible effects on bone mechanical properties [14].

Although collagen has long played second fiddle to mineral with regard to skeletal fragility, mounting evidence suggests that the age- and disease-related alterations in collagen content and structure may be important

contributors to fracture risk (see previous review by Burr [16]). Theoretical analyses indicate that the soft protein phase in "biocomposites" plays a key role in alleviating impact damage to mineral crystals and to protein/mineral interfaces [17]. Additional support for the view that collagen plays an important role is provided by the observation that polymorphisms in the COL1A1 gene are associated with altered bone material properties and increased fracture risk independent of BMD status [18, 19]. Further support is provided by the finding that an increase in the urinary ratio between native and age-related forms of collagen type I degradation products is associated with increased fracture risk independent of BMD and partly independent of bone turnover rate [20]. In contrast to collagen, much less is known about the contributions of other extracellular matrix components to bone quality [21].

- Discussions during the symposium clarified that additional research in this area is needed to
- Determine the relationships between mineral crystal properties and bone mechanical behavior
- Determine the effect of osteoporosis therapies on mineral crystal and collagen properties
- Determine the interaction between various collagen properties and bone mechanical behavior
- Define the nature of the interactions between collagen fibers and mineral crystals and how these interactions affect whole bone mechanical behavior
- Determine how age-, disease-, and treatment-related changes in matrix composition and microstructure affect whole bone mechanical behavior and fracture risk
- Determine the role of noncollagenous matrix proteins in maintenance of skeletal integrity
- Consider the development of new biochemical markers that reflect matrix proteins specific to bone

The impact of remodeling and damage on bone quality

Throughout life, physiologic loading of the skeleton produces fatigue damage in bone. Although the optimal methods to quantify microdamage in bone are subject to debate [22], it is generally accepted that accumulated damage weakens bone and is associated with activation of remodeling. However, the impact of this damage on fracture risk has not yet been established.

Several presentations reviewed the notion that, broadly considered, the functions of bone remodeling are to assist with mineral homeostasis and to maintain structural integrity, both by adapting bone mass and distribution to altered mechanical loading and by repairing this fatigue-induced damage. However, the amount of bone remodeling required to maintain these functions is unknown [23, 24]. Dr. Schaffler suggested that in "healthy" bone there is a balance between expected accumulation of damage due to daily loading and its repair [25]. With this view, too much, as well as too little, remodeling can accelerate microdamage accumulation and lead to fractures.

Data showing increased microcrack accumulation in normal dogs treated with high doses of bisphosphonates have raised concerns regarding the possible risks associated with either oversuppression or long-term suppression of remodeling [26, 27, 28]. In these studies, an increase in microcrack density was accompanied by increased whole bone strength, but reduced toughness. The clinical relevance of these findings was debated during the symposium, as 5- to 7-year treatment of postmenopausal women with amino-bisphosphonates is not associated with an increased risk of fracture [29, 30]. However, it is unclear whether different results would be found in younger, more active women treated with bisphosphonate therapy for a similar duration. Studies are needed to identify the changes in remodeling that upset this critical balance between damage accumulation and repair to an extent where fracture risk is increased.

It is interesting to note that whereas the accumulation of microdamage is associated with reduced mechanical properties, the ability of a material to undergo "microcracking" may actually increase its toughness [31, 32, 33]. As a simple explanation for this latter phenomenon, consider that when a material with a crack in it is loaded, energy is accumulated at the tip of the crack. This energy can either be dissipated by growth of the crack, or by the generation of microcracks near the tip of the larger crack. In this latter case, growth of the larger crack is inhibited, and the material can absorb more energy (i.e., making it tougher) before this larger crack eventually progresses through the material to cause failure. The specific characteristics of bone that confer "good" microcracking versus "bad" microdamage remain to be elucidated.

The discussions at the symposium revealed that much remains to be learned regarding damage accumulation in bone, including how best to measure it, the factors that govern it and its role in skeletal fragility and fracture risk. Participants concurred that additional research is needed to

- Establish clear relationships between microdamage and the array of bone biomechanical properties
- Determine the role of damage in fracture risk, establishing how much matrix damage can occur before mechanical integrity is impaired at a clinically relevant level
- Determine safe levels of remodeling suppression
- Determine how different therapeutic regimens (cyclic, combination and sequential treatment) and cessation of treatment influence microdamage accumulation in vivo
- Further define the relationship between activation frequency and microdamage accumulation

The impact of material and structural heterogeneity on bone quality

The potential impact of heterogeneity versus homogeneity of material and structural properties on skeletal fragility is another issue that was debated during the symposium. Because bone is a composite material with a complex hierarchical organization, there are many levels at which to consider the concept of heterogeneity. Currently, there is no consensus as to the most appropriate methods to quantify material and structural heterogeneity in bone. Dr. Boskey hypothesized that a broad distribution (i.e., heterogeneity) of mineral crystal size would confer optimal bone strength [14]. In addition, Dr. Burr presented theoretical arguments and empirical data showing that homogeneous materials are generally poor at resisting crack growth and therefore have reduced toughness [34]. Nonetheless, the extent and nature of material and structural homogeneity that may impair mechanical integrity at a clinically relevant level have yet to be established.

Heterogenity of bone tissue

Although optimal methods for assessing material heterogeneity have not been established, the distribution of mineralization density values has been used as 1 estimate of the relative heterogeneity of bone material. In contrast to arguments that a more homogeneous material will have decreased resistance to fracture, evaluation of iliac crest biopsies showed that individuals with vertebral fractures have a more heterogeneous distribution of mineralization density values than individuals of similar age without fractures [35]. Individuals with fractures had regions of very low mineralization and regions of extremely high mineralization. This finding suggests that those with fractures may have an impaired capacity to regulate bone remodeling to avoid these extremes of tissue mineralization that are likely to be sites of mechanical weakness [36].

Additional data regarding heterogeneity of mineralization density are provided by evaluation of iliac crest biopsy specimens after osteoporosis therapy. In these studies, the heterogeneity of mineralization density values increases following intermittent PTH therapy [10] and decreases following bisphosphonate therapy [8], yet both treatments are associated with reduced fracture risk. Thus, although theoretical arguments suggest that increasing material homogeneity will negatively impact bone's resistance to fracture, empirical evidence contradicts this view. Clearly, we are just starting to unravel the complex relationships between material heterogeneity, bone quality and fracture risk.

Heterogeneity of bone structure

Evaluating heterogeneity at the structural level may also provide information regarding skeletal fragility. Similar to the situation with material heterogeneity, the best methodologies by which to quantify structural heterogeneity are under investigation. Nonetheless, Ciarelli et al. [37] reported that, although the average trabecular thickness was similar in trabecular bone specimens from the femoral head of hip fracture patients and age-matched control specimens with the same bone volume, the fracture patients had increased anisotropy (i.e., more trabeculae aligned with the axis of primary loading and thus fewer trabeculae oriented in the transverse direction). This relative homogeneity in trabecular orientation—notably independent of bone volume—may have put these individuals at greater risk for fracture during nonphysiologic loading, such as would occur during a fall.

In another example of the potential impact of structural heterogeneity on bone quality, Yeh et al. [38] reported that increased heterogeneity of trabecular microarchitecture was associated with decreased mechanical properties of cancellous bone. In particular, their simulations indicated that increasing the variation in trabecular thickness led to dramatic reductions in stiffness. Importantly, these trends were independent of bone volume fraction, suggesting that both the volume fraction and microarchitectural inhomogeneity may impact bone strength and fracture risk.

Taken together, these observations regarding material and structural inhomogeneity suggest that additional research is needed to

- Develop and validate methods for assessing material and structural heterogeneity
- Determine age-, disease-, and therapy-induced changes in the heterogeneity of material and structural characteristics
- Establish relationships among the heterogeneity of material and structural characteristics, bone quality and fracture risk
- Test whether including not only the average values for traditional morphologic features, such as trabecular microarchitecture, but also their distribution will enhance predictions of skeletal fragility
- Develop noninvasive methodologies to assess material and structural heterogeneity

Assessing bone quality: today and tomorrow

A large body of epidemiologic data indicate that despite its limitations, the current standard for predicting fracture risk is an areal BMD measurement by dual-energy X-ray absorptiometry (DXA) [39, 40]. However, BMD measurements reflect only 1 aspect of bone quality, the quantity of bone per area. Discussions during the symposium highlighted the disparity between the information provided by BMD and that required to improve the diagnosis and treatment of osteoporosis. The proceedings from the symposium offer compelling evidence that

new imaging modalities and biomarkers capable of assessing various components of bone quality have the potential to provide the information required to improve the diagnosis of osteoporosis, prediction of future fracture risk and monitoring of treatment response. This section presents a brief review and critique of current and future noninvasive methods for assessing components of bone quality.

Use of biomarkers to assess bone quality

Currently available biochemical indices of bone turnover, particularly those of bone resorption, predict fracture risk independently of BMD [41, 42] and have been shown to account for a substantial proportion of the reduction in fracture risk following antiresorptive therapy [43]. It is not clear whether these markers directly reflect aspects of skeletal fragility or whether they indirectly reflect skeletal traits, such as increased cortical porosity, cortical thinning and degradation of the trabecular network, that are consequences of increased resorption. It is beyond the scope of this summary to evaluate the potential of biomarkers for assessment of bone quality and fracture risk. However, interested readers are referred to several recent discussions of this topic [41, 42, 44, 45, 46].

However, of particular interest with regard to biomarkers that may reflect characteristics of bone quality is the observation that the ratio of urinary excretion of native and age-related forms of C-terminal cross-linking telopeptides, which reflect the degree of racemization/isomerization of type I collagen, predict fracture risk independently of BMD and partly independently of bone turnover [20]. There is evidence that racemization and isomerization may alter protein structure and function; however, further experimental studies are needed to evaluate the impact of these collagen modifications on bone biomechanical properties. Moreover, additional studies are needed to verify the clinical utility of these measurements.

Use of noninvasive imaging to assess bone quality

The most advanced noninvasive imaging tools are capable of measuring the amount of bone and how it is arranged, but are limited in their ability to assess the intrinsic properties of the bone material itself [47, 48, 49]. Substantial progress has been made in recent years in developing noninvasive imaging modalities capable of assessing bone structure and predicting bone strength. These efforts generally employ 1 of the following approaches: (1) analysis of 2-dimensional DXA measurements to derive bone structure, (2) 3-dimensional imaging modalities, including magnetic resonance imaging (MRI) and computed tomography (CT) and (3) finite element analysis using high-resolution CT or MRI images. A common goal is to determine whether the imaging modality performs as well as BMD, or adds information in addition to that provided by BMD for prediction of bone strength and fracture risk.

An important issue debated at the symposium but as yet unresolved is how much spatial resolution is required. The size of bone structures that one may be interested in range from a few millimeters (for the thickness of the cortex at the distal radius) to a tenth of a millimeter (for the thickness of an individual trabeculae). Yet, it is not known whether it is necessary to accurately measure the dimensions of individual trabeculae to provide better estimates of skeletal fragility and treatment response. There was consensus that the resolution needed to improve clinical evaluations may be less than that desired in basic research. It may not be the improved resolution that is critical, but rather the improved understanding of what features should be measured. Only then can appropriate imaging modalities be developed.

Use of dual-energy X-ray absorptiometry to assess bone structure

Dr. Beck described the approach and limitations of using 2-dimensional DXA scans to derive bone geometry measures at the proximal femur [47]. This method has provided novel information regarding age-, race-, and sex-related differences in femoral geometry that may contribute to hip fracture risk [50, 51, 52, 53, 54, 55, 56]. However, a number of assumptions are implicit in this method, the validity of which has not been established in different patient populations and disease states. Moreover, the method is inherently limited to analyses in a single plane, and therefore cannot fully reflect bone strength. Although this approach is potentially useful when other options are not available, alternative methodologies capable of directly measuring the 3-dimensional geometry, such as MRI and CT, should be developed and employed in clinical studies to better establish the relationships among bone geometry, bone density and fracture risk.

Three-dimensional imaging modalities to assess bone structure

Both MRI and CT have been used to assess 3-dimensional (3D) bone structure [57, 58]. Two approaches for using MRI to assess bone structure have been employed: relaxometry and high-resolution imaging. In the first approach, MRI relaxation parameters of the bone marrow (such as T_2*, the magnetic field heterogeneity relaxation time) are used to provide an indirect assessment of trabecular architecture. To date, this approach has been applied to the calcaneus, distal radius, spine and proximal femur [58, 59, 60, 61]. As evidence of the potential utility of the technique, Wehrli et al. [59] recently reported that MRI relaxation parameters at the

calcaneus discriminated vertebral fracture patients from control subjects better than did BMD measurements. Although the precision of the method is relatively poor, it does not require high spatial resolutions, needs relatively short imaging times and can be applied on current clinically available MRI instruments.

The other MRI-based approach employs the latest high magnetic field clinical scanners combined with specially designed coils to generate images of trabecular architecture at peripheral sites. In vivo resolutions of 100 μm to 300 μm in plane and a slice thickness of 250 μm to 500 μm have been achieved [57, 58]. With this resolution, it is not possible to produce accurate values for most features of trabecular architecture (which range from approximately 100 μm to 200 μm for trabecular thickness to 300 μm to 500 μm for trabecular separation). Nonetheless, the "apparent" trabecular properties derived from these images correlate strongly with measurements of trabecular architecture obtained with higher resolution techniques [62, 63]. These MRI-derived indices differentiate patients with hip and vertebral fractures from control subjects, with the best performance afforded by combinations of structural parameters and BMD [63, 64, 65, 66, 67, 68]. Thus, MR-based imaging of trabecular architecture appears promising as a tool to assess aspects of bone quality at peripheral sites and warrants additional investigation. The current limitations of high-resolution MRI include the relatively long acquisition times (10–15 min), requirement for specialized coils and restriction to evaluation at appendicular sites. Future developments in MRI may alleviate some of these concerns [58].

CT scans of the proximal femur and spine are currently used to assess geometry and volumetric density of the trabecular and cortical bone compartments [69, 70]. This approach employs standard clinical CT scanners in combination with a bone mineral phantom used to calibrate the image data. This type of CT imaging has been applied to clinical studies of intermittent PTH and afforded insights into the mechanisms of this therapy [71, 72, 73, 74]. This technique could easily be used to evaluate the combined effect of changes in bone geometry and density [75]. Advantages to this approach are that it can be employed on standard clinical scanners with relatively short imaging times, although even the minimal radiation exposure is a concern for some subjects.

An alternative CT-based approach involves high-resolution imaging of trabecular bone structure. Although initially images were limited to an in-plane resolution of approximately 400 μm and slice thickness of 1 mm, recently high-resolution imaging with multi-slice spiral CT scanners has achieved an in-plane resolution of approximately 200 μm and slice thickness of 500 μm. This approach has been used in vivo to evaluate the lumbar spine, yet its performance with regard to differentiating patients with and without fractures has not been substantially better than BMD [76, 77]. The latest high-resolution, peripheral CT systems (i.e., in vivo μCT) are reported to achieve resolutions of up to 80 μm at tolerable radiation doses [48]. In contrast to high-resolution CT imaging of the central skeleton, the in vivo μCT technique is promising for accurate assessment of trabecular architecture at peripheral sites. However, it has yet to be rigorously tested in clinical studies. The major drawbacks to further developments with the in vivo μCT technique are that it needs specialized equipment and employs ionizing radiation, which may limit its use in some patient populations.

Finite element analysis of high-resolution images to estimate bone mechanical behavior

Recent studies have demonstrated the feasibility and potential utility of combining high resolution CT and MRI images with finite element analysis methods to assess the effects of bone structure on mechanical properties [78, 79, 80, 81]. For instance, Pistoia et al. [78] reported that μCT imaging (˜165 μm resolution), combined with finite element estimates of bone strength, predicted the failure load of cadaveric forearms considerably better than did BMD. The feasibility of this approach was further demonstrated in 2 recent clinical studies. In the first, high-resolution MR images of trabecular bone in the distal radius were combined with finite element analysis to determine effects of trabecular microarchitecture on bone mechanical properties in normal and osteopenic postmenopausal women [81]. In the second, high-resolution MR imaging of the calcaneus was used in combination with finite element analysis to quantify changes in trabecular bone in response to 1 year of idoxifene therapy [79]. In both cases, the use of finite element analysis provided additional information regarding bone strength compared to that available from structure measurements alone. Thus, this approach warrants further investigation. However, because this technique currently requires extensive computational resources and specialized software, widespread evaluation will likely be limited.

Other imaging modalities

Ultrasound imaging was initially proposed as a technique capable of measuring bone quality [82], yet the transmission ultrasound methods currently used primarily reflect BMD [83]. Several transmission ultrasound modalities have been shown in prospective studies to be predictive of fracture risk, and in this capacity they perform as well as BMD measurements [84, 85]. However, new ultrasound imaging techniques applying acoustic impedance, backscatter and combined reflection and transmission measurements show promise for examination of trabecular structure and material properties [86, 87, 88, 89, 90, 91, 92].

Methods to image the bone matrix noninvasively have proven difficult. In this regard, Wu and colleagues

[93] recently demonstrated the potential of using water- and fat-suppressed projection MRI for noninvasive imaging of bone matrix properties. Although not yet developed for in vivo measurements, this method, in combination with solid state 31P projected MRI [94], may eventually allow for noninvasive assessment of the matrix composition and degree of mineralization. However promising and compelling these current and future imaging modalites may be, they should be considered research tools at present, as most have not been rigorously tested for their ability to predict fracture risk and monitor treatment response. Among those that have been tested in clinical studies, few have performed substantially better than BMD. This relatively disappointing performance may be attributable in part to the fact that decreases in the amount of bone strongly correlate with degradations in trabecular architecture and matrix properties. Thus, for prediction of fracture risk, it may be necessary to move beyond traditional measurements of bone morphology to identify characteristics that are independent of bone density and that can be assessed noninvasively [48]. In turn, imaging modalities capable of assessing trabecular architecture may be particularly useful in assessing subtle treatment-related changes in bone strength. Clearly, additional developments and studies are needed to determine the imaging modalities best suited to assess bone quality for different clinical purposes. The discussions identified that additional research is needed to

- Identify, develop and validate new biomarkers that may complement skeletal imaging techniques
- Develop accurate, reliable methods for 3D estimation of bone morphology
- Improve our understanding of how to characterize bone geometry and strength in individuals of differing body size
- Determine relative importance of bone density versus microarchitecture for prediction of fracture risk, and in particular identify which features of trabecular architecture are most predictive of skeletal fragility
- Determine whether noninvasive measurements of these microarchitectural features provide improved assessment of fracture risk and response to treatment
- Compare effects of different osteoporosis therapies on bone morphology and microarchitecture in humans
- Test whether high-resolution imaging in combination with finite element analysis will improve assessment of fracture risk and response to treatment
- Develop new methods to assess properties of the bone matrix noninvasively

Conclusions

In conclusion, decades of research have provided insights regarding the causes and consequences of skeletal fragility, but many questions still remain unanswered. Despite the success of BMD measurements as a diagnostic tool, there is room for improvement regarding the identification of those at greatest risk for fracture and monitoring the response to treatment. Current therapeutic interventions reduce fracture risk, but do not prevent fractures completely, and therefore there is room for enhancing therapeutic efficacy as well. Unambiguous identification and improved understanding of the specific material and structural components that determine a bone's resistance to fracture will lead to improved diagnostic tools and novel therapeutic agents. Whereas ongoing studies will address many of these unresolved questions, the issues are complex and additional research is still needed.

In the end, our goals are high:

1) to understand the relative contributions of the various aspects of skeletal fragility on fracture risk in vivo,
2) to develop new diagnostic methods that can identify the specific causes of skeletal fragility within an individual patient,
3) to develop novel therapeutic agents targeted at those aspects of skeletal fragility that most strongly influence fracture risk and,
4) to offer interventions (pharmacologic and nonpharmacologic) designed to treat causes of skeletal fragility that are specific to the individual patient.

Achievement of these goals will require continued collaborations between biologists, physicists, materials scientists, engineers and clinicians, will involve basic, translational, clinical and epidemiological research strategies and will require cooperation (and funding) from public, private and industrial groups. It will be essential to establish partnerships between industry groups and federal funding agencies, with the goal of incorporating novel tools for assessing skeletal fragility in ongoing and future clinical trials. Due to the rapidly growing proportion of elderly persons worldwide, combating the diseases and consequences of aging is among the most compelling medical burdens facing societies today. Thus, solving the mysteries of skeletal fragility is a compelling and worthy goal for the next decade and beyond.

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