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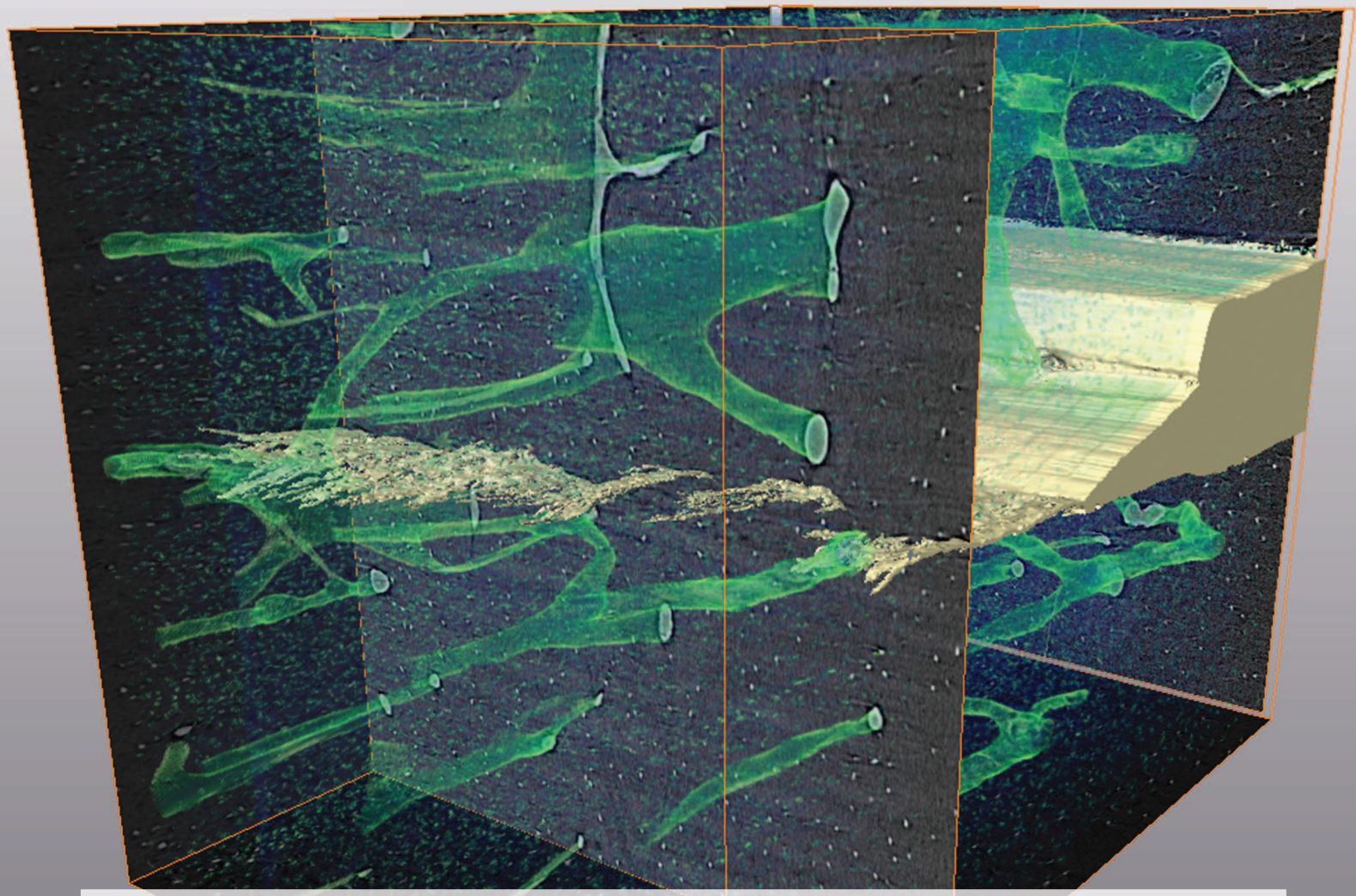

BONE

On page 1287, E. A. Zimmermann and R. O. Ritchie discuss how human cortical bone's hierarchical structure resists deformation and crack growth through physics-based mechanisms at small and large length-scales, which are essential to resist fracture. Using synchrotron micro-computed tomography, the three-dimensional structure of human cortical bone, with its vascular canals at the center of each osteon (in green), can be observed resisting the propagation of a crack (in yellow) through crack-tip shielding mechanisms, such as uncracked ligament bridging.

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Bone as a Structural Material

*Elizabeth A. Zimmermann and Robert O. Ritchie**

As one of the most important natural materials, cortical bone is a composite material comprising assemblies of tropocollagen molecules and nanoscale hydroxyapatite mineral crystals, forming an extremely tough, yet lightweight, adaptive and multi-functional material. Bone has evolved to provide structural support to organisms, and therefore its mechanical properties are vital physiologically. Like many mineralized tissues, bone can resist deformation and fracture from the nature of its hierarchical structure, which spans molecular to macroscopic length-scales. In fact, bone derives its fracture resistance with a multitude of deformation and toughening mechanisms that are active at most of these dimensions. It is shown that bone's strength and ductility originate primarily at the scale of the nano to submicrometer structure of its mineralized collagen fibrils and fibers, whereas bone toughness is additionally generated at much larger, micro- to near-millimeter, scales from crack-tip shielding associated with interactions between the crack path and the microstructure. It is further shown how the effectiveness with which bone's structural features can resist fracture at small to large length-scales can become degraded by biological factors such as aging and disease, which affect such features as the collagen cross-linking environment, the homogeneity of mineralization, and the density of the osteonal structures.

1. Introduction

Natural materials, which invariably are composites comprising both organic polymers and mineral components, have impressive mechanical properties that have specifically evolved to match a desired function. Collagen-based tissues, such as bone, teeth, skin, cartilage, antler, and fish scales, to name a few, are a prime example. These tissues all share a common motif of collagen molecules at the nanoscale; however, they have evolved different hierarchical features (e.g., microstructures, graded material properties, interfaces), or nanoscale profiles (e.g., mineralization or cross-linking), to meet their different mechanical needs.[1] The differentiation in the higher level structures allows a suite of mechanical specialties including superior toughness values, as in the case of antler with its low mineralization,[2,3] or penetration resistance as in the sophisticated graded material properties found in fish scales.[4,5]

In the face of the mechanical evolution of natural materials to their specific function, engineers have many lessons to learn on materials design. However, the superiority of natural composites to man-made engineered materials lies in the fact that their overall mechanical properties are invariably far better than those of their individual constituents.[6] In this respect, the key feature of natural composites is their hierarchical structure consisting of distinct structural features from the nano to macro levels.[7] This multi-scale hierarchical structure, where the structure at each level is tailored to local needs, allows the adaptation and optimization of the material form at each level to meet specific functions. Indeed, biological systems represent an inexhaustible source of inspiration to materials scientists in offering potential solutions for the development of new generations of structural and functional materials.[8]

In terms of natural composites, human cortical bone is one of the most intriguing materials as it serves as a damage-tolerant structural framework for the human body with the ability to adapt and repair itself.[9] Bone's mechanical properties allow it to resist fracture in a variety of physiological loading conditions, as a direct result of its hierarchical structure (**Figure 1**), which resists deformation and fracture through physical-based mechanisms at the nano- and microscale.[10]

This review reports recent advances in our understanding of the mechanical integrity of human cortical bone. Here, the critical features of bone's complex structure are addressed as well as their mechanistic role in generating fracture resistance. One key to our understanding of the generation of bone's mechanical properties is to investigate how it responds to its physiological environment. We therefore give examples of how mechanisms resisting bone fracture in its hierarchical structure react under multi-axial loading and high strain rates. Another aspect of bone's mechanical properties is how aging and disease increase fracture risk through biological degradation to the structure. Here, we review recent advances on how aging, vitamin-D deficiency, osteogenesis imperfecta, and

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Paget's disease can adversely affect bone's mechanical integrity. Accordingly, from the lessons learned studying the structure and mechanical properties of bone in healthy and disease states, we hope to gain insight into how perturbations in the bone-matrix nano/microstructure can affect bone's damage tolerance.

2. Hierarchical Structure of Human Cortical Bone

Human cortical bone's unique mechanical properties stem from its hierarchical structure, which spans some seven architectural levels from the individual collagen molecules and mineral platelets to the whole bone (Figure 1).[9] The structure of bone at its smallest length-scale is composed of organic and mineral components, namely type I collagen and hydroxyapatite, respectively. These two components form a composite structure at the nanoscale. Here, collagen molecules form an array, such that adjacent collagen molecules are staggered by 67 nm (Figure 1). Mineral platelets with an approximate size of 50 nm × 50 nm × 2 nm form in the gaps between the heads and tails of the collagen molecules.[12,13] Within the gaps, the *c*-axis of the mineral's hexagonal crystal structure is aligned parallel to the long axis of the collagen.[14] Besides the gap zones, further mineralization occurs on the surface of the fibril.[15–17] Overall, this composite structure of collagen and mineral is termed a mineralized collagen fibril and is the basis of many biological mineralized tissues from tendons and skin to hard mineralized tissues, such as bone, teeth, antler and fish scales.[1]

Cross-links play an important role in stabilizing the arrangement of collagen molecules. Immature enzymatic cross-links (DHLNL and HLNL)[18] between collagen molecules presumably stabilize their 67-nm periodicity.[19,20] As the bone tissue matures, the cross-link profile changes. The "immature" intermolecular enzymatic cross-links between the collagen molecules are converted to "mature" non-reducible cross-links (i.e., pyridinoline and pyrrole) between neighboring fibrils. [19,21] In addition to enzymatic cross-links, non-enzymatic cross-links, known as advanced glycation end-products (AGEs), occur in bone. AGEs may be a critical aspect of the bone structure because their accumulation has been linked to bone fragility in aging and diabetes. AGEs occur via a glucose-mediated reaction and form intra- and interfibrillar connections.[19] As the non-enzymatic cross-links are not site-specific, their magnitude can markedly increase with age. Indeed, the enzymatic cross-link profile is known to reach a steady-state around 10–15 years of age, while AGEs can increase up to five-fold with age.[21–24]

The mineralized collagen fibrils hierarchically assemble into fibers (≈1-μm diameter), while the fibers assemble into lamellae (≈5 μm-thick sheets) to form osteons, which are the most prominent motif on the microstructural scale (Figure 1). The osteons are nominally cylindrical with a circular cross-section of roughly 200 μm in diameter. Their central vascular channel, the Haversian canal (≈90 μm in diameter), is concentrically surrounded by lamellae.[25] At the outer limits of the osteon is a 5-μm thick border called the cement line, which separates individual osteons from surrounding tissue. The cement line contributes to the heterogeneity of the microstructure and the generation of toughness, as its composition is either collagen-deficient or highly mineralized compared to surrounding tissue.[26]

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3. Toughening Mechanisms in Human Cortical Bone

The hierarchical nature of human cortical bone's structure is key to generating its mechanical properties of strength and toughness.[10,27] In terms of materials design, strength and toughness are generally mutually exclusive: to improve strength, plasticity is generally suppressed, while to improve toughness, plasticity is promoted. However, bone's hierarchical structure can develop strength and toughness independently. Indeed, the mechanical integrity of bone can be thought of as

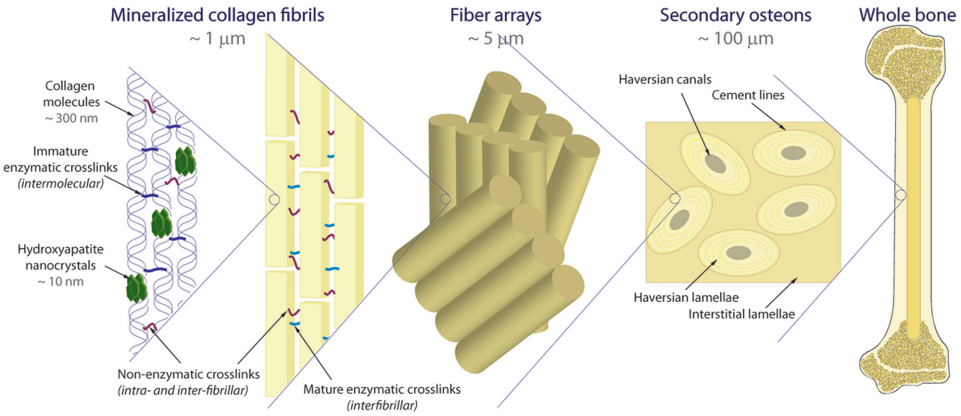


Figure 1. Hierarchical structure of human cortical bone. Bone and other natural materials are able to generate their unique combination of strength and toughness from their hierarchical structure spanning nano- to macro-scale features. The dense cortical bone is mainly found within the diaphysis of long bones and the shell surrounding the porous trabecular bone. At the microstructural level, the cortical bone consists of cylindrical features called osteons, which are roughly 250-μm wide. At the center of the osteon is a vascular channel termed the Haversian canal, which is concentrically surrounded by lamellae. At the outer bounds of the osteon is an interface of material called the cement line with a higher content of mineral. The lamellae consist of arrays of collagen fibers, which are assembled from arrays of collagen fibrils. The fibril is a composite of collagen and mineral. Essentially, an array of collagen molecules is stabilized with cross-links as well as mineral nanoplatelets embedded in between the heads and tails of the collagen molecules. Reproduced with permission.[11] Copyright 2011, National Academy of Sciences.

a competition between intrinsic and extrinsic mechanisms.[29,30] The intrinsic mechanisms stem from the material's inherent resistance to elastic and inelastic deformation and originate from the structure at small (nanoscale) length-scales. They are active ahead of the crack tip to alleviate damage principally through the generation of plasticity. Conversely, extrinsic mechanisms do not actually change the inherent material toughness but rather operate mainly in the wake of the crack tip solely to inhibit crack growth by "shielding" the crack from the full applied driving force; this is achieved through interaction of the crack path with principally micrometer-scale structural features (**Figure 2**).[29,30]

Fracture events in bone encompass initiation and growth of cracks as well as the resulting complete fracture of the tissue. Thus, toughness or resistance to fracture is a critical part of bone's mechanical integrity. The toughness of bone can be measured through fracture-mechanics techniques, which characterize the fracture toughness or 'crack driving force' as a function of crack extension, Δa, that is, the crack-growth resistance curve (R-curve).[31] Materials exhibiting extrinsic toughening, such as bone, display rising R-curves, where the toughness increases as a function of crack extension (**Figure 3**).[32] One consequence of rising R-curve behavior is that measuring a single-value toughness, such as the plane-strain fracture toughness K_{Ic},[33] does not fully characterize material behavior. The full R-curve, i.e., the crack-driving force defined in terms of K, G or J,[34] as a function of Δa is the only faithful representation of the toughness behavior (Figure 3).[32] The crack-initiation toughness can be defined at the start of the R-curve, i.e., at $\Delta a \rightarrow 0$, and provides a measure of the intrinsic toughness; the maximum value or slope of the R-curve is defined as the crack-growth toughness and provides a measure of the extrinsic toughness. Here, we focus on how the mechanical properties of healthy human cortical bone originate from a combination of intrinsic and extrinsic toughening mechanisms acting in concert at multiple length-scales throughout the structure.

3.1. Intrinsic Toughening Mechanisms

The intrinsic resistance to fracture can be experimentally measured through the crack-initiation toughness during a fracture-mechanics test or as the yield or ultimate stress in a strength test. In bone and other biological materials, the scale of the mineralized collagen fibril is where intrinsic fracture resistance is generated. Here, we overview the various mechanisms responsible for such toughening in bone.

3.1.1. Intrafibrillar Toughening Mechanisms

As the fibril is bone's basic building block, its mechanical behavior under elastic and inelastic deformation is an important basis for bone's overall mechanical integrity. Previous experimental and molecular-dynamics studies on unmineralized collagen fibrils indicate that during elastic (recoverable) deformation, fibrils deform through stretching of collagen arrays.[35,36] Small-angle X-ray scattering (SAXS) on mineralized tissue, which measures fibrillar deformation during a mechanical test, also confirms fibrillar stretching in the elastic region as the fibrillar strain linearly increases with the applied tissue strain.[11,37,38] In contrast, during plastic deformation, molecular-dynamics studies predict unmineralized collagen arrays to exhibit molecular stretching and uncoiling as well as stretching of the gap regions.[39,40] In mineralized tissue, however, the presence of mineral in the collagen fibril limits the deformation in the gap region to increase the fibril stiffness.[39] Besides the degree of mineralization, other variations in the nanostructure may also contribute to fibrillar deformation, such as cross-linking between the collagen molecules, which may promote fibrillar stretching.[41,42] Thus, in mineralized tissues such as bone, the deformation mechanisms within the fibril are most likely dominated by stretching of the collagen-mineral composite structure. However, further studies are required to define

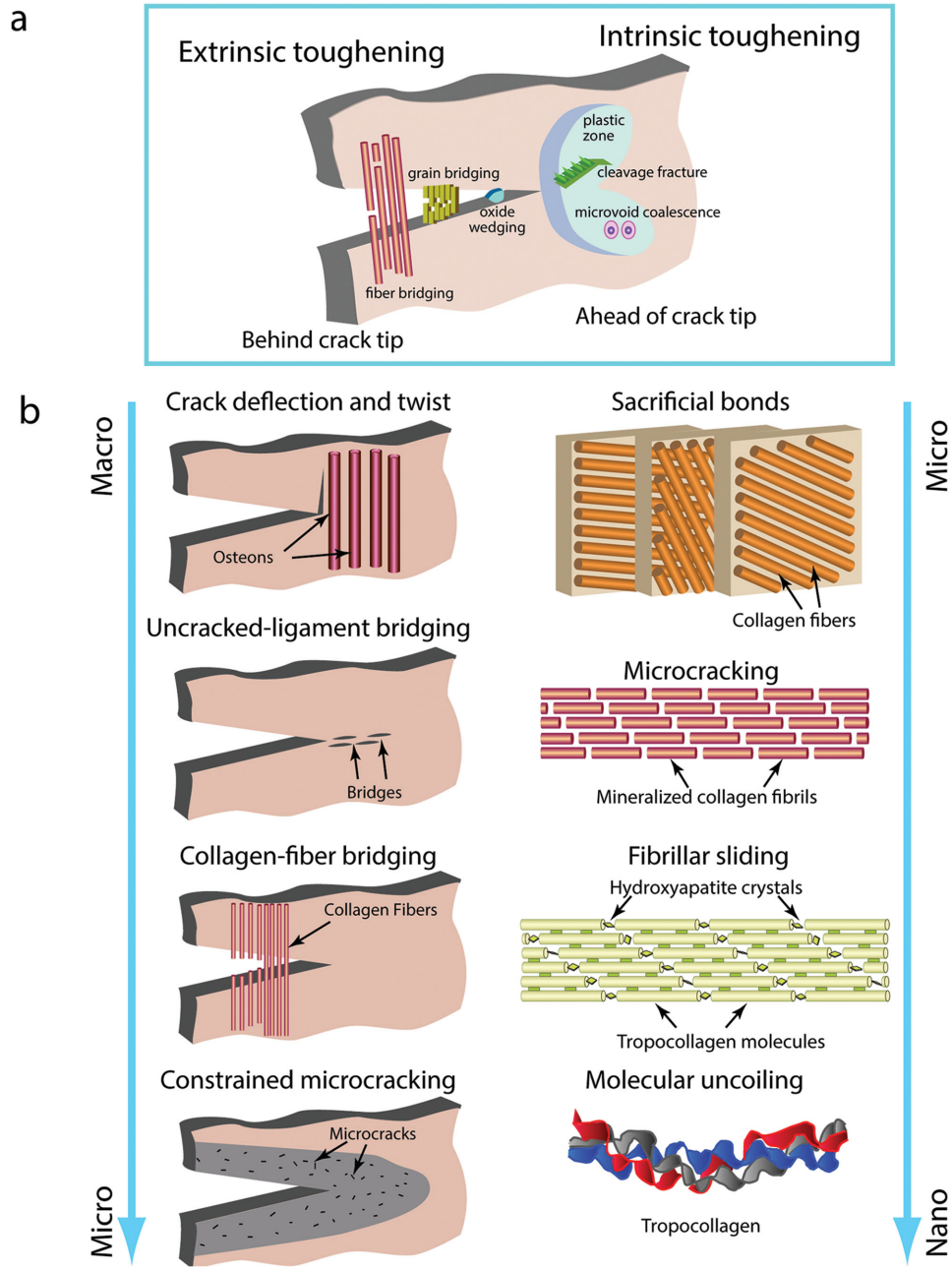


Figure 2. Toughening mechanisms in bone. a) Bone's resistance to fracture can be described as a competition between intrinsic toughening mechanisms, acting ahead of a crack tip to promote principally plasticity to resist microstructural damage and extrinsic crack-tip shielding mechanisms that mainly act behind the tip of a growing crack specifically to resist crack propagation. b) The intrinsic mechanisms mainly contribute to toughness at small length-scales through inelastic deformation within the collagen-mineral composite, sliding between fibrils, and sacrificial bonding. Additionally, larger structural features, such as the osteonal structures and networks of collagen fibers, are able to interact with a growing crack and shield the crack tip through mechanisms of crack bridging and/or the deflection and/or twisting of the crack path. Adapted with permission.[28] Copyright 2010, Annual Reviews.

precisely how fibrillar deformation is influenced by variations in mineralization, cross-linking and other nanoscale characteristics.

3.1.2. Interfibrillar Sliding

The ability of bone to plastically deform is apparent from strength tests. For a long time, bone's plasticity was ascribed to the presence of collagen. However, as we begin to better understand how load is transferred within bone's structure, we see that the hierarchical nature of bone, which allows deformation between length-scales, may contribute more to its time-dependent behavior than solely collagen's mechanical properties. Indeed, recent studies on unmineralized collagen fibrils indicate that the hierarchical structure is actually more viscous and able to generate more plasticity than the

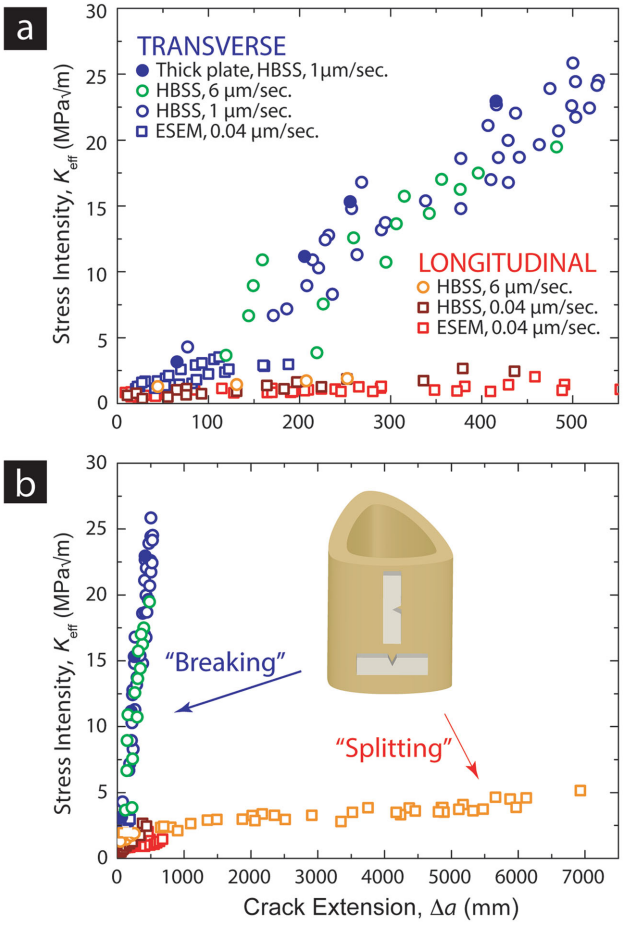


Figure 3. Crack-growth resistance behavior in bone. The toughness of human cortical bone increases as a crack extends due to the creation of extrinsic toughening mechanisms. As such, a single value measurement of the toughness cannot completely characterize the material behavior. Instead, a stress intensity can be measured to sustain subcritical cracking as a function of crack extension, Δa, from a starter notch or crack, which is called a crack-growth resistance curve or R-curve. Example R-curves are shown for the extension of a) short (sub-μm in length) and b) long (mm to cm in length) cracks in the longitudinal (splitting) and transverse (breaking) directions in humerus bone. The R-curve behavior originates from the hierarchical structure's interaction with the crack path through the mechanisms of extrinsic toughening such as crack bridging and deflection/twist, mainly at large length-scales that are able to shield the crack tip from the full stress intensity. Clearly, cracks oriented in the transverse orientation are able to generate more toughness during crack extension than the longitudinal orientation, due to the potency of such active shielding mechanisms, principally arising in this case from crack deflection at the osteonal interfaces. Adapted with permission.[32] Copyright 2008, Nature Publishing Group.

collagen molecules alone.[36,43] Similarly, in mineralized collagen fibrils from human bone tissue, plasticity has been observed to occur through fibrillar sliding. Essentially, as strain is applied to the bone, SAXS experiments show that the fibril's strain linearly increases in the elastic region, before reaching a constant value as plastic deformation begins, even though the whole sample is continuing to deform.[11,37,38] Thus, plasticity is generated by fibrils remaining at a constant strain but slipping past one another, facilitated by sacrificial bonds that break and reform. Changes in the collagen environment, especially cross-linking between fibrils, can play a key role in resisting the sliding process by constraining the allowable deformation.[11]

3.1.3. Sacrificial Bonding

Another region in the bone structure that may facilitate plastic deformation is the bonding between hierarchical length-scales (i.e., collagen molecules, fibrils, fibers, lamellae). In between fibrils, fibers or lamellae, a "glue" exists in the form of molecules, non-collageneous proteins or collagen fibrils, which links the hierarchical length-scales.[44–46] Sacrificial bonds are thought to resist deformation through stretching within the proteinous "glue" that separates the different layers and interfaces,[47] causing the bonds to break and reform in the osteopontin layer that surrounds the collagen fibrils, thereby absorbing energy during the deformation process.[45] Overall, sacrificial bonding provides important contributions to the intrinsic toughness by facilitating plasticity through deformation between different length-scales in bone's hierarchical structure.

3.2. Extrinsic Toughening Mechanisms

Crack-growth resistance (Figure 3) occurs because a growing crack activates extrinsic mechanisms that locally shield the crack from the driving force. In bone, the presence of the osteonal structures with their lamellae and interfaces ("cement lines") generates extrinsic toughness at the microstructural scale by interacting with the crack path. Indeed, the potency of extrinsic toughening mechanisms scales with the size of the structural features shielding the crack, and thus the larger length-scales, generally ≈1–100s μm, are primarily most effective. Here, we overview the various mechanisms responsible for the extrinsic toughness of bone.

3.2.1. Constrained Microcracking

Microcracking is a commonly observed phenomenon in bone, with microcrack densities of 0.11 cracks/mm^2 reported in healthy tissue.[48] Microcracks represent damaged tissue, yet through their formation, the tissue absorbs deformation energy (it represents a form of inelasticity) and potentially signals resorption of damaged areas.[49,50] Microcracks mainly occur along interfaces in bone, primarily at the cement lines, which form the outer osteonal boundaries.[51,52] These regions are susceptible to cracking because of their higher mineralization compared to the surrounding bone matrix.[26] While microcracking no doubt plays a key role in bone's mechanical integrity, there is debate as to whether microcracking plays a direct role in generating extrinsic toughness. Constrained microcracking is a well-known extrinsic toughening mechanism in ceramics and rocks, which are inherently brittle classes of materials.[53] It occurs when microcracks form in the

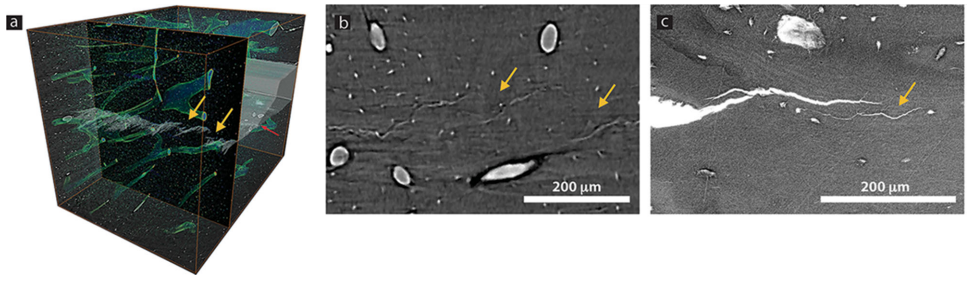


Figure 4. Crack briding promotes extrinsic toughness. The R-curve behavior of human cortical bone originates from extrinsic toughening mechanisms that shield the crack tip. In the longitudinal orientation, especially, crack bridges play an important role. These bridges are intact material spanning the crack wake, often generated by microcracking ahead of a main crack tip (leaving so-called "uncracked ligaments"). a) The 3-D synchrotron computed microtomography image of a fracture toughness sample after testing shows how the crack (grey) grew from the notch (red arrow) and in relation to the Haverisan canals (green). In the crack wake, the yellow arrows indicate the intact material spanning the crack wake. b) The same crack bridges are also apparent when looking at individual slices from tomography that are in a plane perpendicular to the crack growth direction and c) as as part of "mother and daughter" cracks in the scanning electron microscope while monitoring crack extension during mechanical testing. Reproduced with permission.[11] Copyright 2011, National Academy of Sciences.

highly stressed region near the tip of a growing (macro)crack (a microcracking zone). When the microcracks form, they must open or dilate; the increase in volume due to this dilation is constrained by the less microcracked (and hence less dilated) regions surrounding this zone. Thus, the dilating microcracks effectively apply a local compressive stress on the crack wake, akin to a residual stress, which in turn reduces the stress intensity at the crack tip.[53] While this mechanism is significant in certain geological materials, calculations show that constrained microcracking has a minimal effect on the extrinsic toughness in bone.[54] However, the tissue's ability to microcrack does act in a more important way by facilitating the generation of other extrinsic mechanisms, notably crack deflection and "uncracked-ligament" bridging which are the major sources of toughness in bone.

3.2.2. Crack Bridging

Crack bridging is a common form of extrinsic toughening in many monolithic and composite materials. Essentially, as a crack begins to extend, material can be left intact, or uncracked, behind the extending crack tip and hence spans the crack wake. These intact "bridges" carry load that would otherwise be used to further propagate the crack (**Figure 4**),[55] that is, crack bridging locally shields the crack from the full (global) stress intensity, thereby increasing the extrinsic toughness. Crack bridging is an important toughening mechanism in cortical bone, where bridges take the form of uncracked matrix or collagen fibrils. In many biological materials, fibrils can be observed in the crack wake but their contribution to the extrinsic toughness is thought to be relatively small.[54] On the other hand, larger uncracked regions of bone matrix spanning the crack wake ("uncracked ligament" bridging) can significantly enhance the toughness (Figure 4). In bone, uncracked ligaments occur due to microcracking ahead of the growing crack resulting in so-called "mother and daughter" cracks. The matrix in between the microcracks, usually on the scale of 10's µm, spans the crack wake to induce bridging. During crack growth in the longitudinal (splitting) orientation, such uncracked-ligament bridges are the primary toughening mechanism. In this orientation, where the crack grows nominally parallel to the osteons, microcracks easily form along the weak interfaces (i.e., the lamellar interfaces or hyper-mineralized cement lines), leaving regions of intact matrix remaining between the main growing crack and the microcracks initiated ahead of it.[44]

3.2.3. Crack Deflection and Twist

Crack deflection/twist is yet another extrinsic shielding mechanism in bone that allows significant toughening to be generated with crack extension. In mechanical terms, a crack should ideally follow the path maximizing the mechanical driving force, that is, the path of maximum strain-energy release rate G or where the mode II stress intensity[56] is zero, that is, $K_{II} = 0$. However, the path of the crack can make in-plane deviations (i.e., deflections) or out-of-plane deviations through the thickness (i.e., twists) as it interacts with microstructural features. While a straight crack path would maximize the mechanical driving force, the crack deflections or twists result in a lower local driving force at the crack tip. Thus, the toughness is effectively increased as higher applied stresses are required to sustain further crack extension.[32,57,58] Crack deflection/twist can have a significant effect on toughness, particularly in the transverse orientation in bone, increasing it extrinsically by a factor of two or more. In most materials, deflections and twists occur due to features of the microstructure, primarily interfaces or local regions of hard, brittle or less fracture-resistant material. In cortical bone, crack deflections and twisting cracks most commonly result from crack path/microstructural interactions, particularly where growing cracks encounter osteons (**Figure 5**). Thus, this mechanism is particularly effective when bone is loaded in the transverse orientation, where the crack path is nominally orthogonal to the osteonal orientation. The interfaces of the osteons, the hyper-mineralized cement lines, provide a prime location for cracks to markedly deflect. A deflected crack path results in rough fracture

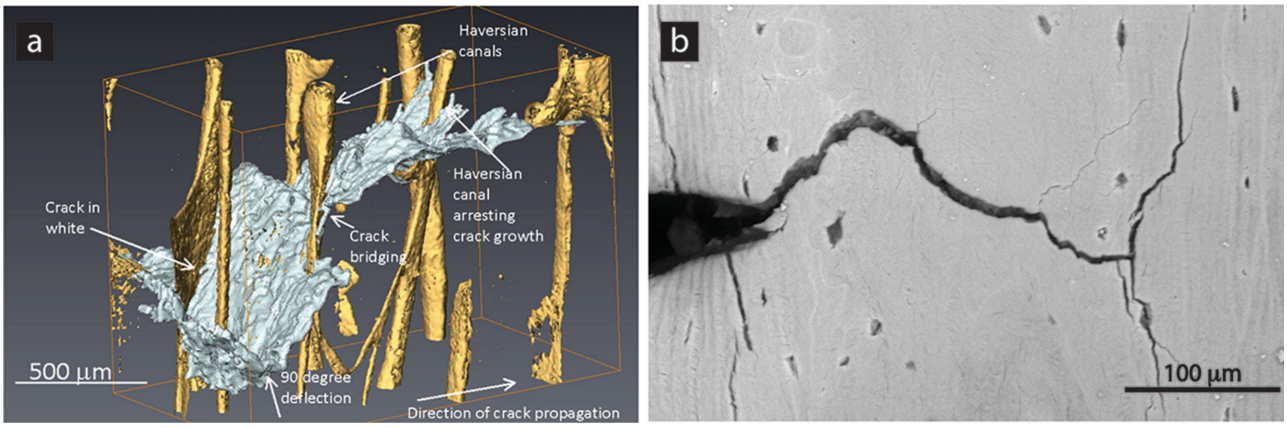


Figure 5. Crack deflection and twist promote extrinsic toughness. When the growing crack is oriented nominally perpendicular to the osteons and Haversian canals in human cortical bone, crack deflection/twist is particularly important. Here, the aligned interfaces within the osteon (i.e., the cement lines and lamellae) provide an interface where the crack often deflects as it grows. Crack deflection increases the toughness of bone because the local stress intensity at the crack tip requires a higher driving force for further crack extension. a) 3-D synchrotron computed microtomography of a fracture toughness sample after testing illustrates how a crack (white) can grow from a notch in a wavy character with deflections and twists as it encounters the osteons. b) Crack deflections are also visible when using scanning electron microscopy during crack extension.

surfaces that are generally characteristic of high toughness.[32] For this reason, bone is invariably significantly tougher in the transverse ("breaking") orientation than the longitudinal ("splitting") orientation (Figure 3).

4. Bone Toughness Under Physiological Conditions

From the nano-composite structure of the collagen and mineral to the sacrificial length-scales and interfaces between hierarchies, the structure of human cortical bone is an engineering marvel. Indeed, many details about the structural assembly and the origins of the mechanical properties are still unknown. Here, we review recent work addressing how the cortical bone structure resists physiological conditions, such as multiaxial loading and high strain rates.

4.1. Role of Multiaxial Loading

Bone invariably fractures under complex loading conditions, involving combinations of tension, shear and torsional loading. However, mechanical property measurements generally only involve tensile loading conditions. These idealized conditions are used because they generally generate the worst-case scenario for most materials.[59–61]

Mixed-mode loading at a crack tip is produced from combinations of mode I (tension), mode II (shear) or mode III (anti-plane shear) crack-tip displacements (**Figure 6**). The mixed-mode loading conditions can be generated by the character of the applied force, the shape of the bone, and/or the orientation of the crack in relation to the far-field load. The toughness under mixed-mode loading can be evaluated in terms of a critical value of the strain-energy release rate, G_c, where G is defined in terms of the mode I, II, and III stress intensities (respectively K_I, K_{II}, and K_{III}) as follows:

$$G = \frac{K_I^2}{E'} + \frac{K_{II}^2}{E'} + \frac{K_{III}^2}{2\mu} \quad (1)$$

where μ is the shear modulus and $E' = E$ (Young's modulus) in plane stress and $E/(1-\nu^2)$ in plane strain (ν is Poisson's ratio). For the case of mixed-mode I+II, the combined mode I tension and mode II shear loading can be defined in terms of the phase angle, $\Psi = \tan^{-1}(K_{II}/K_I)$, where K_{II}/K_I is referred to as the mode-mixity.

Using this mixed-mode fracture-mechanics framework, the "worst case" toughness value for bone is not always attained under tensile (mode I) loading (i.e., at $\Psi = 0$), which is contrary to most material behavior. [57,58,62] In the longitudinal orientation, the toughness is highest under shear (mode II) loading (**Figure 7**a). However, in the transverse orientation, the toughness is highest under tensile (mode I) loading (Figure 7b). This orientation-dependent toughness of bone results from a competition between two forces influencing the crack path (**Figure 8**): the direction of the maximum mechanical driving force and

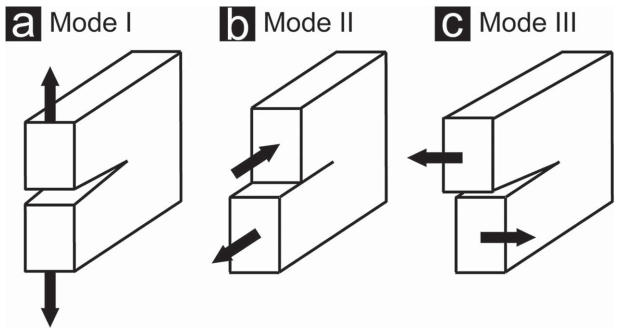


Figure 6. Mixed mode loading. During crack extension, the driving force applied to a crack tip can be broken down into a) mode I tensile displacements, b) mode II in-plane shear displacements, and c) mode III out-of-plane shear displacements. Reproduced with permission.[57] Copyright 2009, Elsevier.

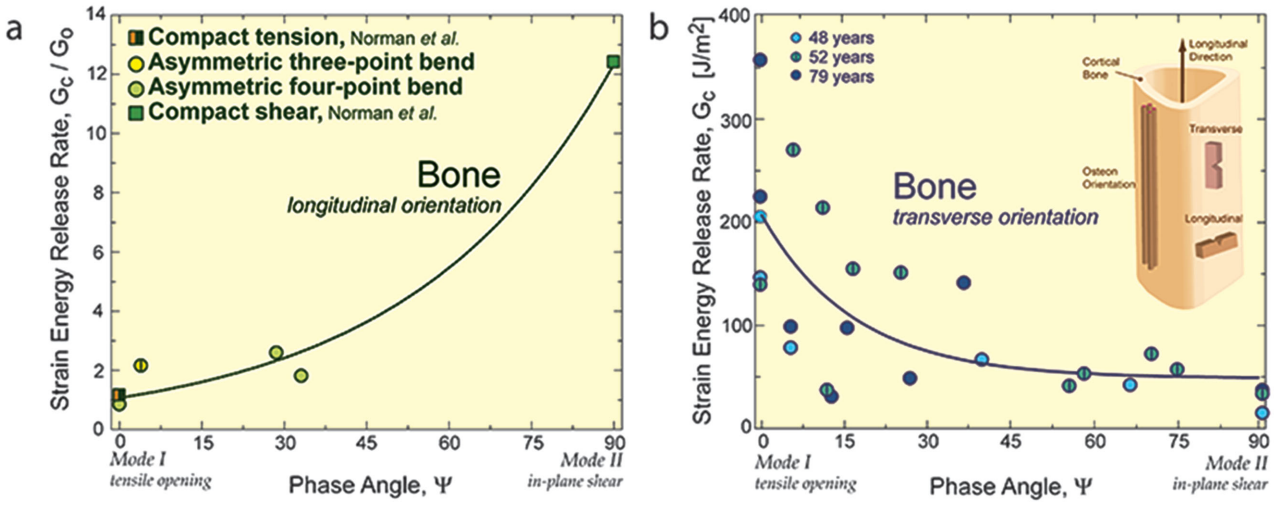


Figure 7. Mixed-mode fracture of bone. The fracture toughness of human cortical bone under multiaxial loading conditions is highly dependent on the orientation of the bone in relation to the loading direction. a) For the longitudinal orientation in bone, the toughness is lowest under mode I, tensile loading,[64] while b) in the transverse orientation, the toughness is lowest under mode II shear loading. These results are a consequence of a competition between the two factors that control the trajectory of cracks, specifically between the preferred path of the maximum driving force, for example, the path of maximum strain energy release rate G (or where $K_{II} = 0$), and the path of least microstructural resistance. Adapted with permission.[57] Copyright 2009, Elsevier.

the orientation of the 'weakest' path in the bone-matrix microstructure.[57,58,62] The preferred path based on the driving force will tend to drive the crack along a path of maximum G (or $K_{II}= 0$). Thus, under mode I conditions, the preferred crack path is straight (i.e., a deflection of 0°), whereas at the extreme mode II condition, the preferred crack path will cause a deflection of 74° to the original crack plane.[63] As cracks tend to follow the cement-line interfaces, the direction of preferred (microstructural) crack paths in relation to the orientation of the loading always plays a critical role in determining the toughness in bone.

Thus, the toughness of bone is lowest when the preferred directions of the microstructural crack path and the driving force are commensurate. This situation occurs in longitudinal orientation under mode I, where the orientation of the structure is parallel to the driving force (0°) and in the transverse orientation in mode II, where the structure is perpendicular to the original crack and the preferred mechanical path is around 74°.[57,58,62] Toughness values are high when the two crack path criteria are incommensurate, such as for human cortical bone in the transverse orientation in tensile loading conditions (Figure 8). Here, complex fracture patterns, with markedly deflected cracks and a correspondingly elevated toughness are generally observed. It is for this reason that bone can display a higher toughness in tension than in shear, a surprising result at first glance but one which implies that the fracture resistance of bone should not be solely evaluated in mode I.

4.2. Role of High Strain Rates

The majority of clinical bone fractures occur as a consequence of traumatic injury. While such events inevitably produce complex mechanical loading conditions, the underlying

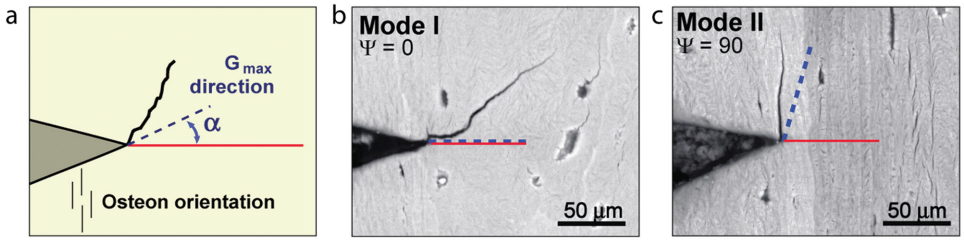
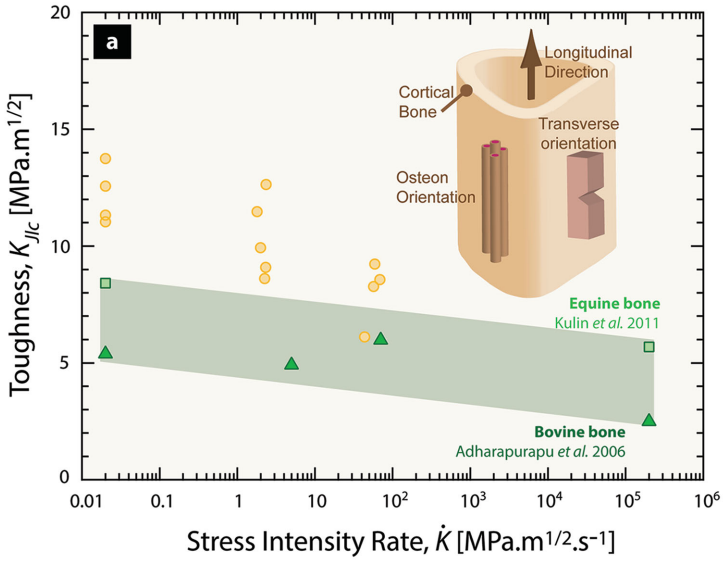


Figure 8. Crack paths in multiaxial loading. The resulting toughness and crack path under multiaxial loading are a result of the preferred path of least microstructural resistance, which generally follows the orientation of the osteons, and the preferred path of the driving force, e.g., the maximum G path, which will vary from 0° for mode I and 74° for mode II fracture. For the transverse orientation, a) the orientation of the osteons is perpendicular to the original crack. Here, the red line represents the original orientation of the crack and the dotted line represents the preferred direction of the driving force. b) In mode I, the preferred direction of the driving force is parallel to the original crack. The resulting crack path is nominally straight. Additionally, the toughness is higher because the preferred directions of the microstructure and driving force are incommensurate. c) However, in mode II, the direction of the driving force is at a 74° angle with respect to the original path of the crack. This configuration results in a low toughness because the preferred path of the driving force and the structure are nearly aligned. Adapted with permission.[57] Copyright 2009, Elsevier.



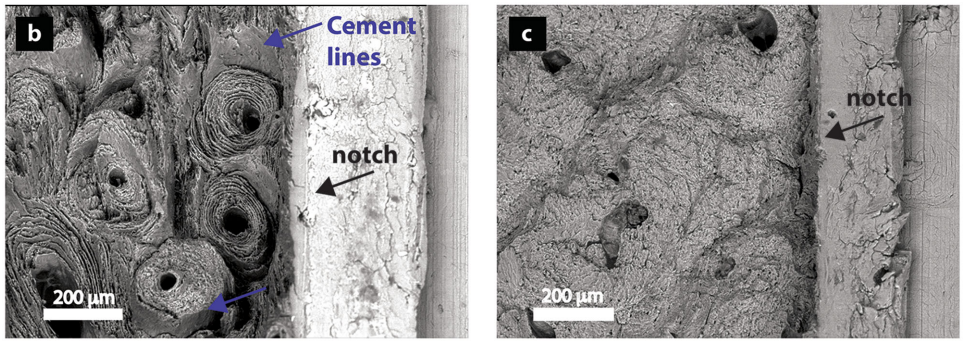


Figure 9. Toughness of bone at high strain rates. a) The toughness of human cortical bone progressively decreases as physiologically higher strain rates are approached. By analyzing the fracture surfaces of the toughness specimens, b) the crack clearly takes a tortuous path around the outer boundary of the osteons (i.e., the cement lines) at slow strain rates. c) However, at the highest strain rates, cracks no longer deflect along these cement lines. The absence of the extrinsic toughening mechanism of crack deflection at high strain rates acts to diminish the fracture resistance of bone. Adapted with permission.[68] Copyright 2014, Elsevier.

commonality is that most bone fractures occur at relatively high strain rates. In the literature, however, the majority of studies address the mechanical properties of bone at relatively low strain rates, prompting recent studies to address how the bone structure resists fracture under a range of physiological loading conditions, to determine whether the characteristics of the salient intrinsic and extrinsic toughening mechanisms are rate-dependent.

The fracture toughness of bone is known to diminish as the strain rate is increased (**Figure 9**a).[65–68] At the microstructural scale (≈10–100s µm), distinct changes in the path of the crack through the bone-matrix structure are apparent at different strain rates. At lower strain rates, cracks deflect at the cement-line boundaries creating a tortuous path (Figure 9b), whereas at higher strain rates cracks tend to penetrate across the face of the osteons creating a straight crack path with little evidence of crack deflection along the osteonal interfaces (Figure 9c). The lower bone toughness at higher strain rates is thus consistent with the absence of crack deflection, which is a prime mechanism of extrinsic toughening in bone; this implies that toughening mechanisms in bone may be rate-dependent.

To explain why the crack path would change so dramatically from deflecting to penetrating the cement-line boundaries, we use the He-Hutchinson[69] theoretical framework for a linear-elastic crack impinging on an interface between two dissimilar materials. Here, the behavior of the crack as it encounters the interface depends on the elastic modulus mismatch of the materials across the interface and the relative toughness of the bone matrix to the cement line (**Figure 10**). Based on the interface toughness, $G_{interface}$, the toughness of the osteon, G_{osteon}, (i.e., the bone matrix) and the relative elastic mismatch, the crack will arrest at the interface if the material properties put it below the critical line in Figure 10 and will penetrate the interface if it lies above. At different strain rates, the toughness of the highly mineralized cement line interface and the relative elastic modulus should remain relatively constant. Thus, to pass from the crack arresting to crack penetrating region in Figure 10, the high strain rate conditions must decrease the toughness of the osteon (i.e., the bone matrix) causing it display less plasticity (i.e., intrinsic toughness).[70] Thus, the rationale for the lower fracture toughness at high strain rates (i.e., the extrinsic toughness) from the straighter crack paths

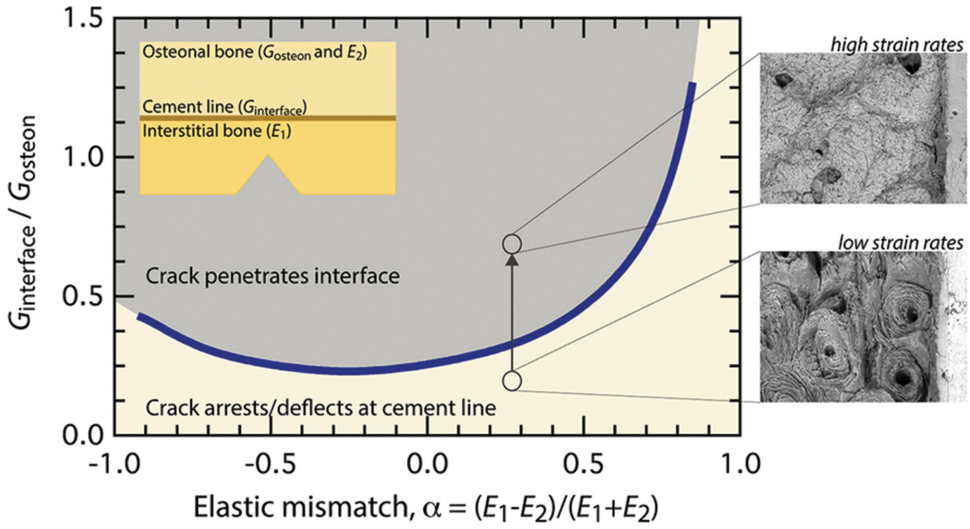


Figure 10. Conditions for crack deflection at an interface. The He and Hutchinson criterion[69] for the conditions for a crack penetrating, as opposed to arresting at, or delaminating along, an interface between two dissimilar (linear elastic) materials, termed 1 and 2, depends on i) the elastic (Young's) modulus E mismatch of materials across the interface, which is defined by the first Dundurs' parameter $\alpha = (E_1 - E_2)/(E_1 + E_2)$, where the subscripts refer to the two materials, and ii) the ratio of the toughness of the interface, expressed in terms of the strain-energy release rate $G_{interface}$, to the toughness of the material into which the crack will propagate, G_{osteon}.[69] At low strain rates, bone begins below the critical line, where the conditions are right for crack deflection at cement lines. However, our observations of fracture surfaces suggest that at high strain rates, the cracks no longer deflect but penetrate the interface, which suppresses the extrinsic toughening mechanism of crack deflection. In order to move into the "crack penetrating the interface" domain, the toughness of the bone matrix must be lower at high strain rates, which we believe originates from lower intrinsic toughness in the form of reduced ductility due to the viscoelastic "lock-up" of the material at high strain rates limiting the extent of plasticity from fibrillar sliding (see Figure 11). Reproduced with permission.[68] Copyright 2014, Elsevier.

is tied potentially to the intrinsic toughness at much smaller length-scales.[68]

To investigate smaller length-scale intrinsic changes to the bone matrix at high strain rates, the fibrillar level mechanical deformation can be investigated using SAXS.[68] At slower strain rates, a linear relation between the fibrillar and tissue strains indicates that the fibril first deforms through elastic stretching (**Figure 11**). Next, the fibril strain reaches a plateau indicating inelastic deformation (e.g., via fibrillar sliding). In higher strain rate tests, the fibril strain vs tissue strain relationships display a higher slope (Figure 11) indicating that more deformation occurs within the fibril; in other words, high strain rates cause the fibril to dissipate energy primarily through elastic stretching and less through inelastic deformation mechanisms (e.g., fibrillar sliding). Essentially, the viscoelastic/time-dependent nature of the mineralized collagen fibril constrains the development of inelastic mechanisms at higher strain rates.[68]

Bone has often been regarded as a viscoelastic material due to the mechanical nature of collagen, a major constituent of bone. However, new evidence suggests that the viscoelastic

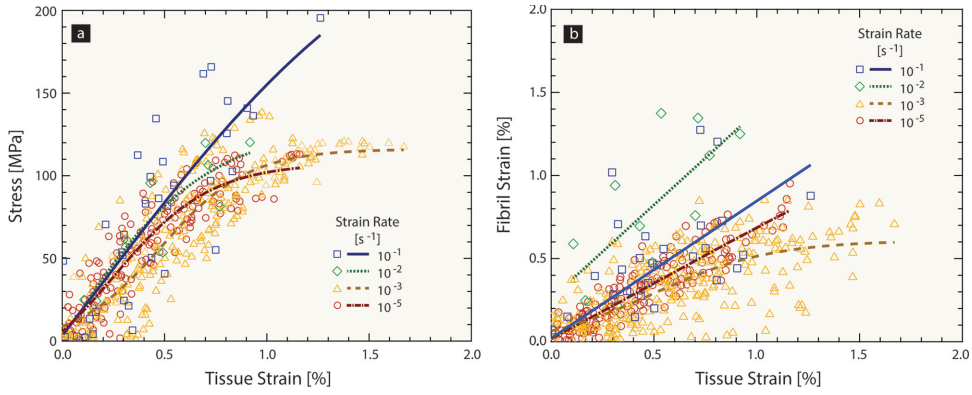


Figure 11. Fibrillar deformation at high strain rates. The deformation at the fibrillar level during high strain rates was evaluated using in situ synchrotron small-angle X-ray scattering (SAXS) measurements during uniaxial tensile tests on human cortical bone samples. a) The stress-strain curve for the bone samples was measured during the tensile tests and indicates a lower degree of plasticity in the samples tested at high strain rates. b) Indeed, deformation in the fibril, measured through changes in the d-spacing of collagen fibrils with SAXS, shows that high strain rates have higher levels of fibril strain. This implies that at high strain rates, plasticity mechanisms, such as fibrillar sliding, are suppressed. Reproduced with permission.[68] Copyright 2014, Elsevier.

properties of bone may actually derive from its hierarchical structure.[36,43] Here, time-dependent or viscoelastic mechanisms may arise from the arrangement of collagen and mineral within the fibril, the assembly of fibrils, sacrificial length-scales, and the opening of dilatational bands or microcracks, which all allow bone to deform inelastically primarily through sliding within and between fibrils.[11,38,45,71] Thus, at slower strain rates, the fibrils attain a certain amount of plasticity and energy absorption through sliding mechanisms within and between fibrils, whereas at higher strain rates these sliding mechanisms tend to lock-up, thereby restricting plastic deformation.

In effect, high strain rates compromise the overall fracture resistance of bone by restricting fibrillar sliding through rate-dependent viscous effects at the nanoscale, which reduces the intrinsic toughness. This in turn affects the ability of cracks to deflect at interfaces, resulting in a lower extrinsic toughness at the microscale. Further studies are still required though to fully understand this coupling between length-scales, particularly in light of very recent evidence of the presence of "dilatational bands", i.e., tiny ellipsoidal voids that form between the mineral aggregates and osteocalcin and osteopontin proteins surrounding the collagen fibrils.[71]

5. Bone Toughness with Aging and Disease

As described above, bone's mechanical properties of strength and toughness are acquired through toughening mechanisms generated at multiple length-scales in a structure which has adapted to the specific needs of the skeleton. Indeed, perturbations to the structure caused by aging or disease can be directly linked to higher fracture risk. Here, we elaborate how some of the biological degradation processes, specifically aging, vitamin-D deficiency, osteogenesis imperfecta, and Paget's disease, can affect the fracture resistance of bone.

5.1. Aging

With age, bone clearly suffers a deterioration in its mechanical integrity. The cause of such an aging-related increase in fracture risk is thought to be a combination of factors causing a loss in bone quantity and a reduction in bone quality.[72,73] In clinical settings, dual emission X-ray absorption, which provides a so-called T-score based on bone-mineral density, or X-ray tomography, which provides the 3-D spatial distribution of bone architecture and mineral content, are used to assess bone quantity. While the loss in bone mass (or bone-mineral density) with age is the clinical standard used to diagnose osteoporosis, bone mass is not the sole predictor of fracture risk.[73] Indeed, bone quality encompasses other tissue characteristics that can influence its resistance to fracture, including the composition and distribution of mineral and collagen, the characteristics and structural integrity of each hierarchical length-scale (i.e., osteon size and distribution), as well as the extent of microdamage.[74] There is now ample evidence that aging-related changes in bone quality at multiple length-scales corroborate the loss of fracture resistance due to a multi-scale deterioration in structure.[11,75]

5.1.1. Aging-Related Loss in Intrinsic Toughness

At bone's smallest length-scales where the tissue consists of a composite structure (i.e., fibril) of collagen molecules and mineral nanoplatelets, aging can alter the cross-linking profile. Here, non-enzymatic cross-links, AGEs, which form due to a glucose-mediated reaction between amino acids in the collagen, progressively increase with age,[22–24] and have been strongly associated with increased fracture risk.[76] Recent studies have addressed how aging-related changes to bone's structure at small length-scales affect its mechanical behavior at the fibril level.[11] To address the fibril mechanics, synchrotron radiation SAXS and wide-angle X-ray diffraction (WAXD) have been used to investigate young and aged samples. Bone's periodic nano-scale structure scatters X-rays, with the fibril's structure scattering X-rays at small angles and the mineral's crystalline structure diffracting X-rays at wide angles. Mechanical testing of the bone samples during the SAXS/WAXD experiments changes the characteristic periodicity of the nano-scale structure and thus provides a measurement of the individual strains in the fibril and in the mineral. For young versus aged bone, the aged tissue has a lower fibril strain (**Figure 12**a), which correlates with a three-fold higher proportion of AGEs cross-links in the aged bone compared with young bone (Figure 12b).[11]

5.1.2. Aging-Related Loss in Extrinsic Toughness

As bone ages, its resistance to crack growth severely diminishes (Figure 12c). The deterioration in toughness is particularly marked in the longitudinal orientation, where cracking tends to be parallel to the osteons. For large crack extensions on the order of millimeters, the crack-growth toughness of young (34–41 years old) bone is five times higher than aged (85–99 years old) bone.[11,75] Imaging the 3-D microstructure using synchrotron X-ray computed microtomography (μ-CT) has shown that aged bone samples have a higher osteonal density than young bone, in this case three-fold higher (Figure 12d,e). The aging-related microstructural changes lead to a lower crack-growth toughness because the size of the uncracked-ligament bridges scales with the osteonal spacing. As microcracks primarily form at, or near, the cement lines, when the osteons are closer together, the size of the bridges is decreased along with the potency of the induced toughening. In the transverse orientation, where crack deflection is the dominant mechanism, the toughness also decreases with aging, but not as severely.[77] Here, the higher osteon density causes more frequent crack deflections with a lower toughness. Indeed, the fact that the osteonal density scales inversely with the crack-growth toughness plays a large role in the fragility of aged bone.[11,75]

Summarizing, we can conclude that in addition to a loss in bone mass, the increase in fracture risk with aging can be related to a deterioration in the bone structure over multiple length-scales. The combined effects of a higher proportion of AGE cross-links at the fibril level and a higher osteon density at the microstructural level reduce the mechanical integrity of aged bone. Mechanistically, the cross-links constrain fibrillar

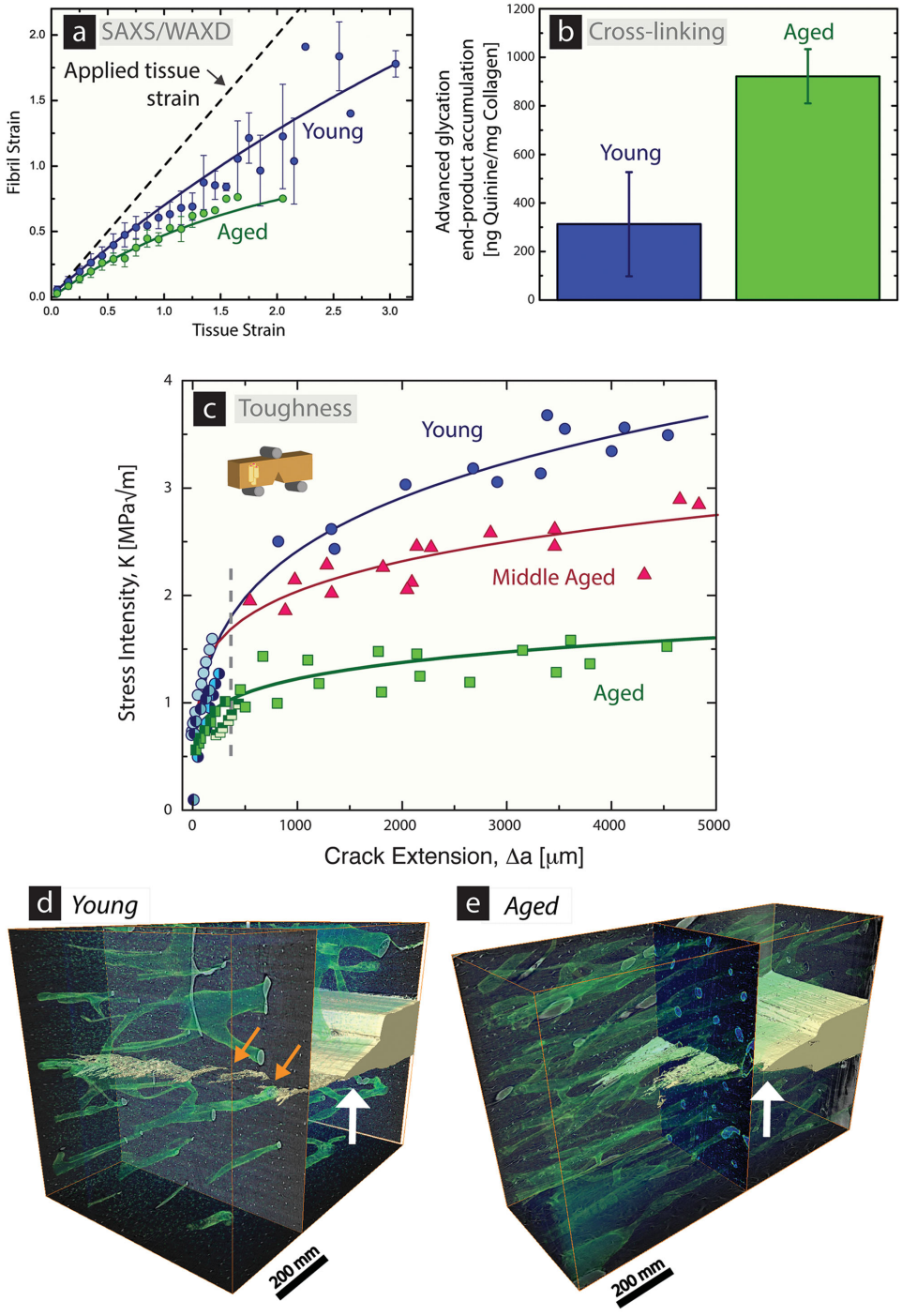


Figure 12. Aging-related changes to bone toughness. With aging, the structure of bone changes at multiple length-scales, which directly affects the bone's mechanical properties. a) In situ SAXS measurements showing that at small length-scales, mineralized collagen fibrils in aged (85–99 year old) bone show far less deformation and ductility than in young (34–41 years old) bone. It is believed that this limited plasticity in older bone is due to cross-linking of the collagen fibrils, as indicated by b) measurements of a three-fold increase in non-enzymatic (AGE) cross-links in aged bone restricting the generation of plasticity at the fibrillar scale (the intrinsic effect). c) Indeed, the initiation and growth toughness of bone decreases dramatically with age.[11,75] Synchrotron computed microtomography of d) young and e) aged fracture toughness samples after crack growth indicates that the large increase in osteon density with age decreases the size and amount of crack bridging allowable in aged bone (the extrinsic effect). Such degradation of both intrinsic and extrinsic toughening mechanisms contributes to the decrease in fracture resistance of human cortical bone with aging. Adapted with permission.[11] Copyright 2011, National Academy of Sciences.

plasticity and the higher osteon density reduces extrinsic toughness during crack extension.[11] These processes can be coupled. With restricted deformation at the fibrillar level from cross-linking, energy can be dissipated by microcracking at higher length-scales. Indeed, aging in bone is associated with an increased density/length of microcracks, which in turn is

the catalyst for the creation of extrinsic toughening by crack deflection and bridging.[11]

5.2. Vitamin-D Deficiency

Vitamin D has an essential role in bone homeostasis, where it aids the absorption of calcium and phosphate.[78,79] A lack of vitamin D can lead to rickets or osteomalacia, resulting in bone pain and a higher fracture risk.[79,80] The clinical hallmark of vitamin-D deficiency is a higher amount of unmineralized bone matrix measured through a bone biopsy. The increased fracture risk has been considered to result from the higher amounts of unmineralized bone matrix.

Vitamin-D deficiency has a marked impact on bone structure. The lower amount of vitamin D restricts calcium absorption, which triggers an increase in bone resorption; specifically, bone deposition is negatively impacted by the lack of vitamin D and consequently calcium. Indeed, the changes in bone remodeling and supply of nutrients cause a high degree of unmineralized bone matrix (osteoid) to cover the surfaces within the bone.[81] While this is known, Busse et al.[82] recently uncovered further aspects of how vitamin-D deficiency impairs fracture risk by characterizing the quality of the mineralized bone matrix lying within the osteoid frame. Using high spatial resolution structural characterization techniques, the mineralized bone was found to have the characteristics of aged tissue.[82] Specifically, in vitamin D deficient bone, the mineralized tissue was found to have a higher cross-linking ratio and carbonate-to-phosphate ratio as measured by Fourier transform infrared spectroscopy (**Figure 13**a,b), which are characteristic of aged tissue. Additionally, synchrotron μ-CT studies showed that the mineralized bone in vitamin-D deficient tissue had a higher degree of mineralization than in healthy bone.[82] The mineralized tissue within the osteoid frame ages due to a key characteristic of bone resorption; the osteoclast cells cannot resorb unmineralized bone matrix.[83] Therefore, the tissue within the osteoid-covered surfaces is essentially trapped leaving aged mineralized bone matrix within an unmineralized frame.

These changes have a marked effect on bone's fracture resistance. Fracture-mechanics measurements revealed a 21% lower crack-initiation toughness in vitamin-D deficient bone and a 31% lower crack-growth toughness, compared to healthy bone (Figure 13c).[82] The extrinsic mechanisms responsible for the lower toughness can be seen by imaging the crack path using synchrotron μ-CT studies (Figure 13d,e). Generally, a more tortuous/deflected crack path indicates a higher toughness, as in the case of healthy bone. However, the vitamin-D deficient bone had straighter crack trajectories with significantly lower crack-deflection angles consistent with its lower toughness. Additionally, crack paths in vitamin-D deficient bone were characterized by far less crack bridging.

Thus, vitamin-D deficiency leads to a "vicious cycle:" bone is resorbed to account for the lack of nutrients but then newly deposited bone tissue cannot be mineralized due to this lack of vitamin D and calcium. This situation leaves an unmineralized layer of osteoid on the surface of bone that in turn cannot be resorbed. The remaining mineralized (i.e., load bearing) tissue is trapped within the osteoid frame, where the collagen and mineral components effectively age. Accordingly, the bone structure displays a lower resistance to crack initiation and growth, characterized by straighter crack paths. Thus,

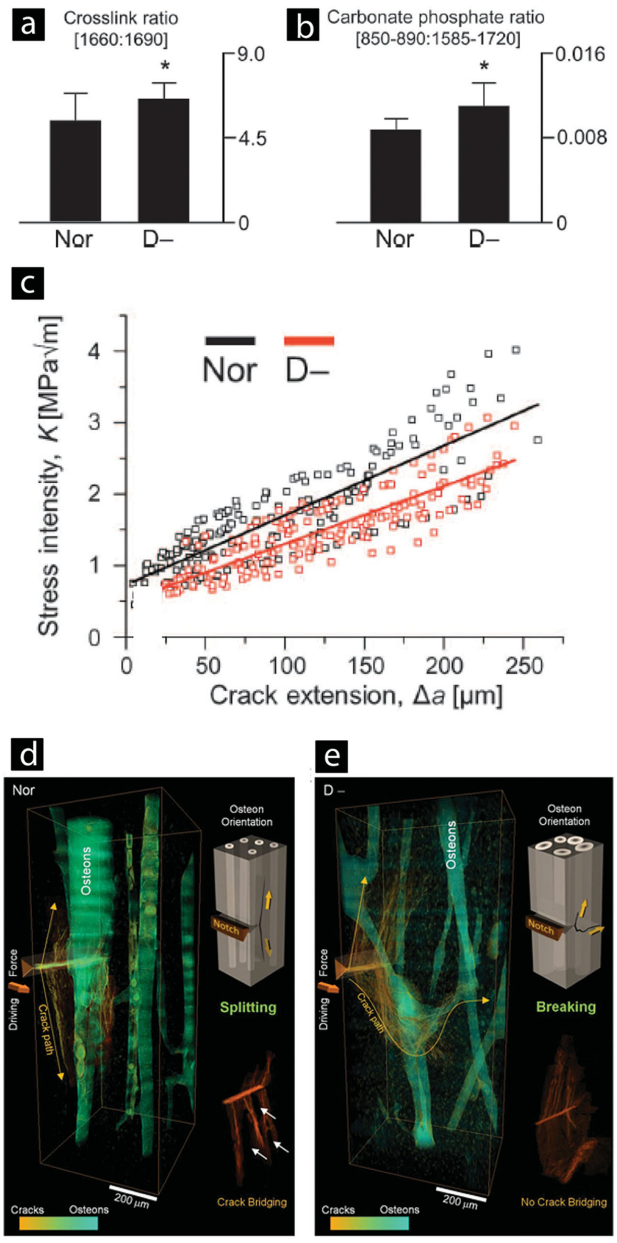


Figure 13. Toughness of bone with vitamin-D deficiency. In vitamin-D deficient human bone (D-), the tissue trapped within the characteristic osteoid-covered surfaces ages, as seen through Fourier transform infrared spectroscopy measurements of a) the collagen cross-link ratio and b) the mineral's carbonate-to-phosphate ratio, as compared to regular healthy bone (Nor). c) The fact that the bone tissue has an aged character results in the loss in the crack-initiation and crack-growth toughness in vitamin-D deficient bone. Indeed, 3-D synchrotron computed microtomography of the crack paths after toughness testing revealed d) crack deflection in the healthy (control) bone compared to e) straighter crack paths in the vitamin-D deficient bone. Adapted with permission.[82] Copyright 2013, American Association for the Advancement of Science.

vitamin-D deficiency changes the bone at small and larger length-scales to limit, respectively, plasticity (intrinsic toughening) and crack deflection/bridging (extrinsic toughening), all of which serves to diminish bone fragility and increase the risk of fracture.[82]

5.3. Osteogenesis imperfecta

Osteogenesis imperfecta (OI), or "brittle bone disease", affects some 1 in 15 000 births and leads to severely increased fracture risk in bone.[84] OI is a result of mutations in the type I collagen, which affect its quantity and structure.[85–89] Clinically, individuals with OI are classified into classes based on the type and severity of mutation. The least severe form of OI is type I, which is characterized by a higher overall fracture risk, while the most severe form is type II characterized by in utero fractures and death.

Currently, the oim mouse model is widely implemented to study OI.[90–92] Oim/oim mice have a similar phenotype as human OI resulting from α1(I) collagen homotrimers that substitute for normal heterotrimer α1(I)2α1(I) collagen.[90] A heterozygous model (*oim*/+) also exists exhibiting heterotrimer and homotrimer collagen and the phenotype of less severe forms of OI.[93]

Mechanistically, the increased fracture risk with OI results from mutations at the molecular level. This has been studied by toughness measurements of the oim mouse model (**Figure 14**a,b), which show that the crack-initiation and growth toughness of the diseased mice decreases with severity of the OI and is associated with corresponding changes in the intrinsic and extrinsic toughening mechanisms.[94] Imaging the crack path with scanning electron microscopy and synchrotron μ-CT reveals crack deflection/twist at lamellar boundaries in healthy wild type mouse bones consistent to that found in most healthy bone (Figure 14c). Conversely, fractures in the oim/oim bone displayed essentially straight (non-deflected) crack paths, nearly flat R-curves and ≈70% lower toughness compared to healthy bone. Indeed, the loss of extrinsic toughening from crack deflection/twist is akin to the presence of woven bone[95] in OI. [90,93,96,97] In woven bone, the disorganized arrangement of collagen and mineral reduces the number of interfaces (i.e., lamellae),[1] thereby lowering the probability of toughening by crack deflection. This is a significant effect as studies on oim/oim bones clearly show that OI bone has essentially minimal resistance to crack extension.

The oim/oim bones also show a significant reduction in intrinsic toughness with the crack-initiation toughness decreasing with OI severity (Figure 14b), consistent with synchrotron SAXS experiments indicating changes in fibril-level deformation.[94] In the oim/oim bones, the homotrimeric nature of the collagen molecules causes kinks and folds in the collagen's structure.[99] The irregular structure of the collagen molecules poses challenges to the formation of the characteristic staggered arrangement of collagen in fibrils. The irregular collagen structure furthermore affects normal mineralization[97,100] as well as enzymatic and non-enzymatic cross-linking of the fibrils.[94,101] Because of this disturbed collagen scaffold as well as the altered nature of the mineralization and cross-links, the ductility of the diseased bone is degraded. These changes in intrinsic toughness are reflected in the reduced crack-initiation toughness of the oim mouse bone and the reduced fibril deformation in SAXS experiments. The lower intrinsic resistance is a consequence of the collagen mutation's effect on the fibril's inherent structure, which in turn leads to defects in mineralization and cross-linking. Therefore, the oim mouse model has a significantly lower intrinsic toughness due to collagen defects affecting the formation of a normal fibrillar structure. Additionally, the extrinsic toughness is reduced due to a larger amount of woven bone, which lacks an oriented structure to deflect cracks and form crack bridges.

5.4. Paget's Disease of Bone

Paget's disease of bone (PDB) is the second most common bone disease after osteoporosis affecting individuals especially over the age of 50.[102,103] PDB localizes at one or more skeletal sites, most commonly the pelvis, spine, femur or tibia.[102–106] In PDB, pathological sites have a strikingly high bone turnover and an overall increase in bone volume.[103,107] The changes to the bone structure result in symptoms of bone enlargement, bowing/deformity, cracking and pain. Indeed, incomplete fractures, termed pseudo or fissure fractures, can be found at sites with severe bowing and deformity.[107–111] Despite the bowing and cracking, the overall fracture risk to patients is low and fracture events at pathological skeletal sites are uncommon (occurring in ≈2% of patients). However, fracture does represent a concern in patients with PDB due to the clear changes in bone fragility.[112–115]

PDB results in a significantly altered bone structure at small length-scales. Specifically, measured using quantitative backscattered electron imaging, the mineral content in PDB bone can be significantly lower, with a higher distribution of low mineralized bone (**Figure 15**a–c).[116] Compositional changes in the tissue are related to the overall stiffness and hardness. Nanoindentation of the PDB cases shows that the pathological tissue has a significantly lower stiffness and hardness, i.e., more plasticity (Figure 15d,e). Thus, the compositional changes in the diseased tissue affect both the elastic (i.e., stretching of bonds generating stiffness) and plastic (i.e., permanent deformation promoting ductility and energy absorption) mechanical properties resulting in a lower stiffness and more plasticity.[116]

Additionally, PDB results in a significantly altered bone structure at the microstructural scale. In the trabecular regions, the elevated bone turnover creates a positive bone balance as reflected by the higher BV/TV (bone volume to total volume) ratio and trabecular number.[103] In cortical regions, instead of the structural patterns characteristic of healthy tissue (i.e., parallel aligned Haversian canals), the pathological tissue is a patchwork of lamellar and woven bone, with less organized collagen fiber orientation.[117–119] Thus, on the microstructural level, trabecular regions densify and cortical regions resemble a dense clumsy bone structure with no well-defined directional collagen fiber or osteonal orientation.

While Paget's disease severely restructures the microstructural organization of bone, the fracture toughness of the diseased cases is not significantly different from healthy bone

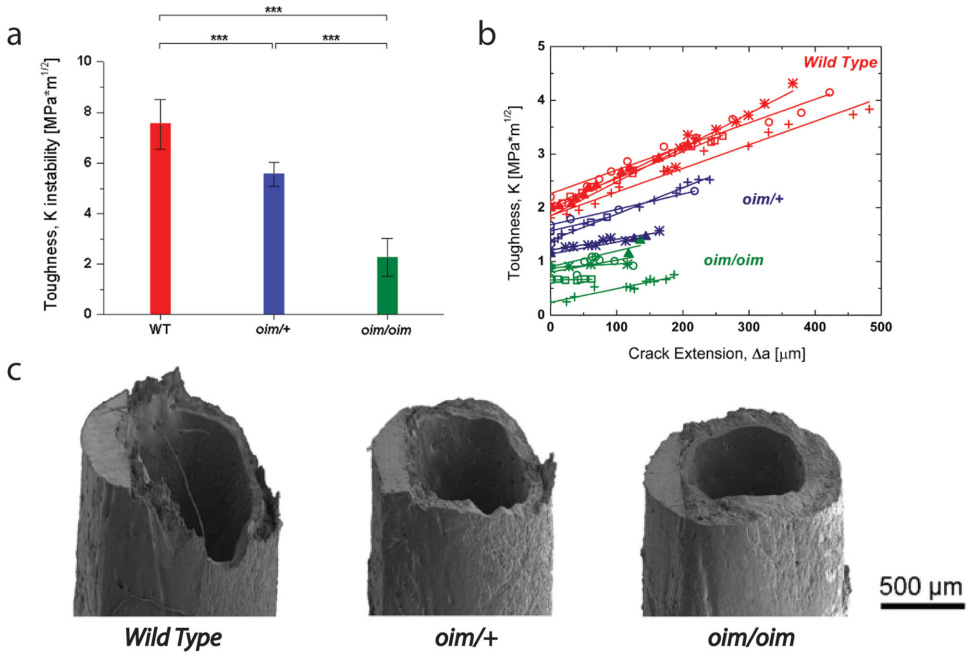


Figure 14. Toughness of bone with osteogenesis imperfecta. The toughness of wild type (healthy) bone, oim/+, and oim/oim mouse femora (oim/+ and oim/oim are mouse models for mild and severe osteogenesis imperfecta) was measured on notched samples in three-point bending using the a) instability method[98] commonly implemented for small animal studies and b) crack-growth R-curves. Indeed, both experimental methods indicate that the oim/oim mouse model has a significantly impaired toughness. c) Specifically, the lower crack-growth resistance, which can be quantified via the slope of the R-curve, correlates with a progressive loss in the crack deflection mechanism with oim severity. Adapted with permission.[94] Copyright 2014, Wiley.

(**Figure 16**a).[116] Although healthy bone resists crack propagation through crack-deflection mechanisms (Figure 16b),[32] human bone from patients with Paget's disease cases exhibits much straighter crack paths (Figure 16c). This seemingly paradoxical observation appears to result from the interplay between intrinsic and extrinsic toughness, which has been a central

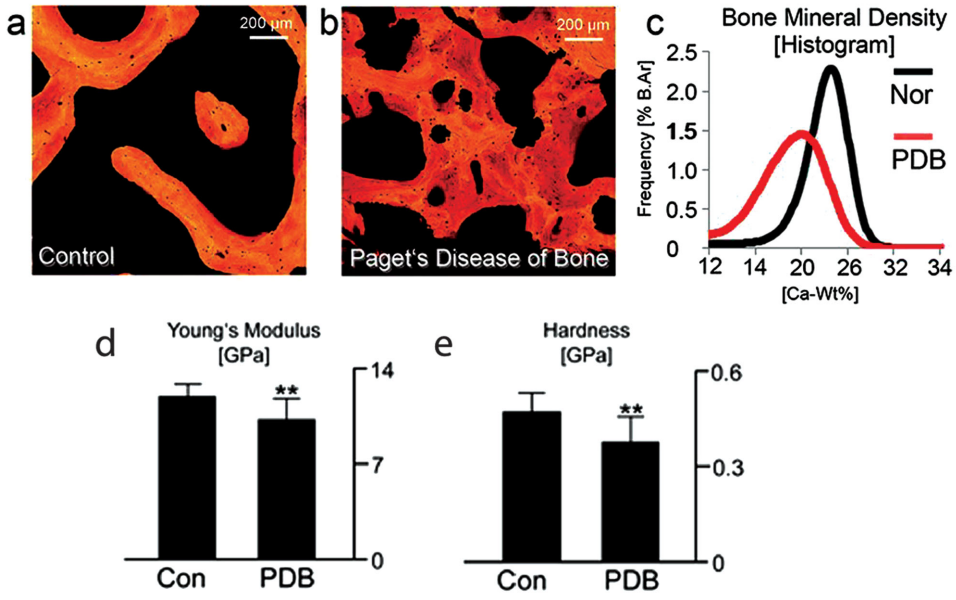


Figure 15. Characteristics of Paget's disease at small length-scales. One of the more dramatic alterations to the bone structure due to Paget's disease is the lower mineralization density distribution. Here, in a scanning electron microscope, quantitative back-scattered electron imaging was performed on bone from the a) control and b) Paget's disease of bone groups. c) Analysis of the distribution of grey values, which correlate to the calcium weight percent, indicates the significantly lower mineralization distribution in Paget's diseased bone. In terms of mechanical properties, the lower mineralization correlates to a significantly lower d) Young's modulus and e) hardness in bone with Paget's disease. Adapted with permission.[116] Copyright 2015, Wiley.

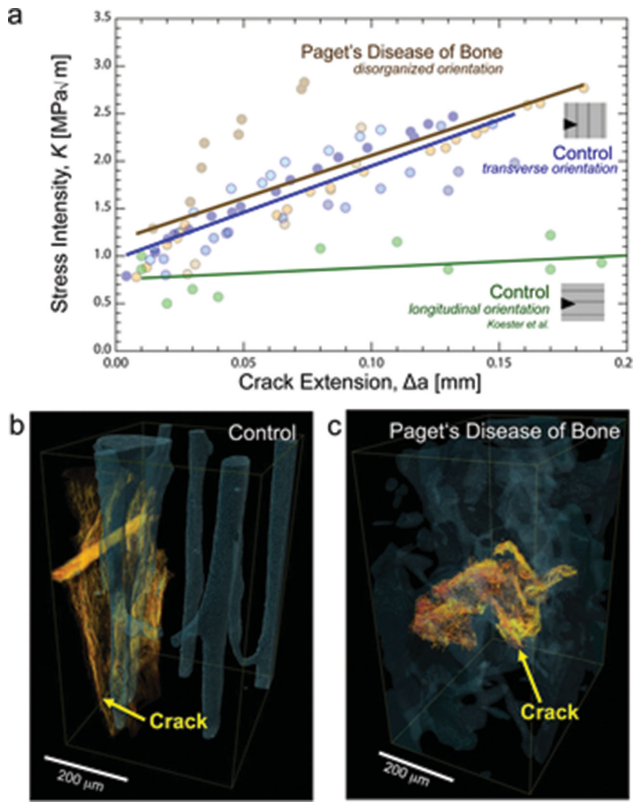


Figure 16. Toughness of bone with Paget's disease. a) Fracture-mechanics tests on iliac crest bone biopsies from control (healthy) bone and that subjected to Paget's disease do not indicate significant changes in the bone toughness with crack extension. b) Imaging of the crack path with synchrotron computed microtomography shows that the control bone displays deflected crack paths, which extrinsically enhances fracture resistance (false color is used to show the crack surfaces in yellow), while c) the Paget's diseased bone displays relatively straight crack paths. Even though crack deflection cannot account for the comparable toughness of bone subjected to Paget's disease, because of its less ordered microstructure, the intrinsic toughening associated with the higher degree of plasticity from the low mineralization may offset this, consistent with the occurrence of stable fractures found in clinical cases. Adapted with permission.[116] Copyright 2015, Wiley.

theme of this review. Even though extrinsic toughening from crack deflection is severely degraded, a possible mechanism for the diseased tissue to generate further mechanical resistance is through plastic deformation, that is, Paget's diseased bone shows higher ductility (intrinsic toughness).[116] Indeed, the Paget's tissue has a lower mineralization and a correspondingly lower hardness, which both indicate that the tissue has the capacity for higher levels of plasticity. Tissues with low levels of mineralization have previously been found to display significant plastic deformation.[2,3] Thus, while toughness is generated through crack deflection in healthy bone (extrinsic toughening), the diseased tissue may generate toughness primarily through intrinsic plasticity mechanisms that promote ductility.

The multiscale characterization of the structure and mechanical properties in Paget's disease provides a basis for explaining some of the clinical symptoms and the overall mechanical integrity of the bone. In particular, the lower spatially resolved mineral content and tissue age of the diseased tissue with a corresponding lower stiffness and lower resistance to deformation could directly account for the occurrence of harmful bone deformities in patients. Additionally, the presence of subcritical (i.e., stable) cracks, so called fissure fractures, in PDB most likely occur due to the bone deformities/bowing. However, the fact that these fractures remain in the tissue and do not cause complete bone failure is in line with the same propensity for the altered structure to resist crack growth through plastic deformation.

The structural changes associated with Paget's disease of bone provide an interesting view into how variations in mineral content and microstructural patterns can influence the mechanical integrity of bone tissue. In particular, this disease state shows the interplay and connections between intrinsic toughening mechanisms at small length-scales, which are primarily plasticity-related, and extrinsic toughening at larger length-scales, which act to "shield" growing crack.

6. Summary

Human cortical bone represents a structural material that through natural evolution of its hierarchical structure has become specifically tailored to resist fracture. Here, intrinsic toughening mechanisms create plasticity and hence ductility in bone through fibrillar sliding processes originating at small, sub-micron, length-scales. Additionally, extrinsic toughening mechanisms operate at larger, microscopic to near macroscopic, length-scales to inhibit crack growth through interactions between the crack trajectory and the microstructure. Indeed, changes to the structure at one or more length-scales can severely curtail the effectiveness of these mechanisms leading to a degradation in the overall mechanical properties and increased fracture risk in bone. Specifically, changes to the cross-link profile due to aging play a significant role in limiting plasticity from fibrillar sliding at the molecular level[11] (irradiation can have a similar effect).[37,120] At larger length-scales, increases in the osteon density associated with excessive remodeling with age can have correspondingly negative repercussions to the extrinsic toughness by limiting the creation of crack bridges.[11,75] Similarly, a reduction in the heterogeneity of the structure of bone, for example, from the abnormal mineralization associated with certain bone diseases,[82,94] can disrupt the relative degree of mineralization in the cement lines compared to the interstitial bone matrix; this can cause far less crack deflection and a consequent loss of fracture resistance. The effects can be enhanced when bone is subjected to high strain rates, where the potency of these toughening mechanisms can be diminished.[68]

We believe that the understanding developed from studies on the fracture behavior of bone can not only aid the diagnosis, prevention and treatment of debilitating bone diseases which specifically target the key microstructural aspects that impart resistance to bone failure, but also provide valuable insight into the design of new structural engineering materials based on the concept of multiple length-scale hierarchical design.

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