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11 MATERIAL AND STRUCTURAL ASPECTS OF BONE IN OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Bone fragility is a fundamental problem in individuals with osteogenesis imperfecta (OI). The mechanisms behind this fragility, however, are not yet well understood. Multiple factors appear to contribute to the increased fracture risk in OI. At the structural level, bone mass deficiency can result in increased stress levels within bones. The underlying mineral and collagen abnormalities that define OI are also believed to result in compromised material-level properties. The variability of collagen biochemical irregularities causing OI and the corresponding heterogeneity of disease severity result in abnormalities that are not easily generalized within the OI population.

The aims of this chapter are to introduce basic mechanical notions pertaining to the strength of structures and materials, and to present a synthesis of existing literature regarding the mechanical properties of bones in OI.

STRUCTURAL MECHANICS

The maximum load that a structure such as a bone can withstand without fracturing is referred to in engineering terms as structural strength. The structural strength of a bone is dependent on its size and shape, how the material is distributed within the bone, the intrinsic (material-level) properties of the bone, and the type of loading.

Physiological loads generally include a combination of four types of loading: tension, compression, torsion and bending (Figure 1). When subjected to these loads, bones will deform by elongating, compressing, twisting, and bending, respectively.

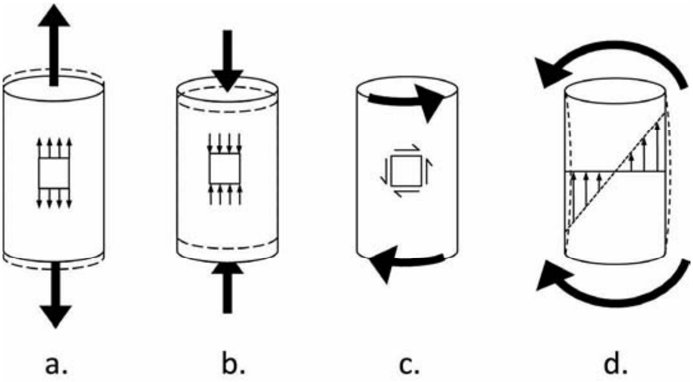

Figure 1. Four major types of loading: tension, generating tensile stresses (a); compression, generating compressive stresses (b); torsion, generating shear stresses (c); and bending, generating a combination of tensile and compressive stresses (d).

When an applied load remains sufficiently low, the structure behaves elastically and the deformation will reverse once the load is removed. The ratio between the load applied and the resulting deformation is called stiffness. For example, under pure tensile loading the ratio between the tensile load and the resulting elongation is the tensile stiffness of the structure. Similarly, under a bending load, the ratio between the applied load and the deformation, i.e., deflection, is bending stiffness.

The load threshold above which a structure will sustain permanent damage is called structural strength. Loosely speaking, stiffness and structural strength are sometimes referred to as "structural properties", although these quantities are not true properties because they are not constant. Instead, they vary greatly as a function of the size and geometry of the structure and the loading configuration. For example, for a structure such as a cylinder or a bone under tension or compression loading, structural strength is equal to the strength of the material itself (this property will be discussed in the Mechanics of Materials section of this chapter) multiplied by the cross sectional area perpendicular to the load. Thus, for a given material, a structure (e.g., bone shaft) with a greater cross-sectional area will be able to withstand greater tensile and compressive loads (Figure 2, left).

In bending and torsion, structural strength is affected not only by the cross-sectional area of material carrying the load, but also by how far away the material is located from a central axis. For example, with a given cross sectional area, stiffness and structural strength in bending and torsion will be higher in for wider bone shaft than for a narrower one, the latter having more bone material situated further from the central axis (Figure 2, right).

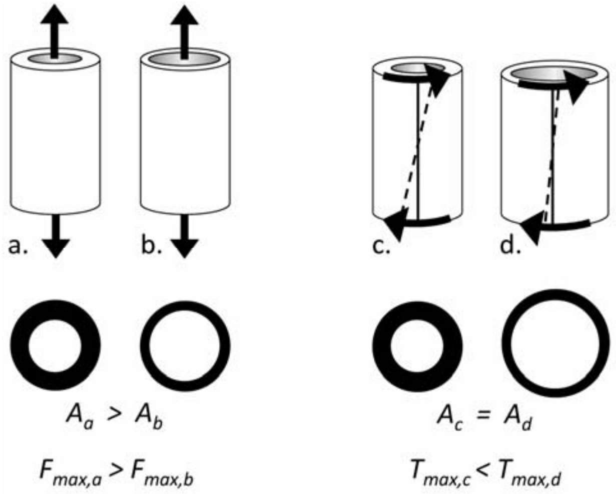

Figure 2. Cylinders in tension (left) and torsion (right). In tension, structural strength, i.e., the maximum force that can be carried without fracture (F_{max}), is proportional to the cross-sectional area (A). If cylinders a and b are made of the same material, cylinder a, having a greater cross-sectional area, will have greater structural tensile strength. Torsional strength, i.e., the maximum torque that can be applied without fracture (T_{max}), is also proportional to how far away the material is located from a central axis. Thus, although cylinders c and d have the same cross-sectional area, cylinder d can resist a higher torque because of its wider diameter.

BONE STRUCTURE IN OI

From a structural perspective, individuals with OI tend to have low bone mass. There is diminished bone density, cortical thickness, and bone shaft diameter. In histomorphometric studies of iliac crest biopsies, reduced amounts of cortical (compact) bone and trabecular (spongy) bone were observed in children with OI when compared with controls.[1,2] Biopsy core width, cortical width, and trabecular bone volume were significantly decreased, and the decreased trabecular bone volume was attributed to a reduction in trabecular number and trabecular thickness. Cortical width and trabecular bone volume was, on average, lower in OI types III and IV than in OI type I.[1]

In the diaphysis (shaft portion) of long bones, where many fractures tend to occur, variable cortical diameters and thicknesses are observed within the OI population. However, individuals with the more severe OI types tend to have narrower diaphyses and thinner cortical shells than do typical individuals. A significant amount of bowing can also develop in children with moderate and severe OI. Having smaller bones and lower bone mass means that there is less bone material to carry applied loads. Individuals with OI can therefore be at a “structural” disadvantage in resisting all types of loads. This disadvantage is most pronounced in individuals with moderate and severe forms of the disorder, for whom the bone volume can be especially low and the presence of bowing can generate additional bending loads.

MECHANICS OF MATERIALS

As discussed earlier, structural strength is a variable measure. Therefore, how can we determine if a level of force is sufficiently low to avoid damage or fracture? To address this question, the engineering concepts of stress and strain are introduced. Let’s first consider a simple type of loading: pure tension. Under a tensile load, a structure such as a rod or a bone will deform by elongating. To predict how much elongation will occur and how much load (force, F) a structure can carry without fracturing, the load and the resulting deformation must be normalized to account for the size of the structure (Figure 3). The normalized load is called stress (σ) and is equal to force F divided by cross-sectional area A. The normalized deformation is called strain (ε) and it is equal to the change in length divided by initial length, For example, if a rod is stretched to 101% of its initial length, it will have a strain of 1%.

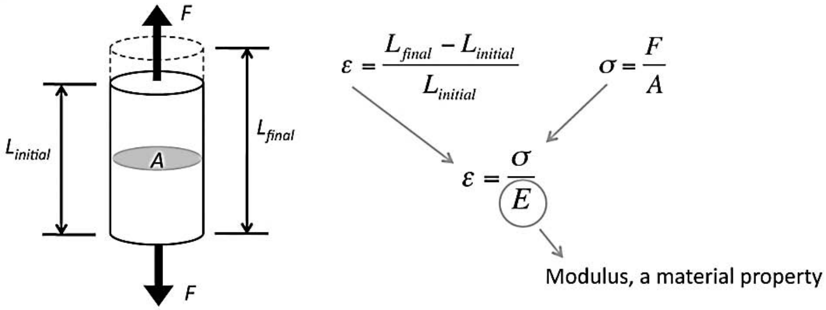

Figure 3. Rod in tension. The relationship between elongation ($L_{final} - L_{initial}$) and applied load (F), is related to the geometry of the rod, i.e., its initial length ($L_{initial}$) and cross sectional area (A), and a material property called elastic modulus (E).

There are three types of stresses: tensile, compressive and shear (Figure 4). Each type of loading results in a different configuration of stresses within a structure (Figure 1). Tensile loading results in tensile stresses, compression loading in compressive stresses, and torsion in shear stresses. Bending results in a combination of stresses. For example, when a straight rod is subjected to bending loads deflection occurs, causing tensile stresses on the convex side and compressive stresses on the concave side (Figure 1d).

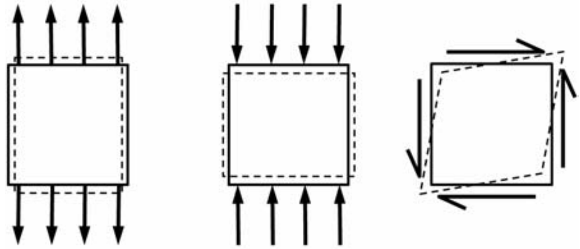

Figure 4. Types of stresses: tensile (left), compressive (center) and shear (right). Each type of stress induces deformation within the material (dashed lines).

In reality, most structures, including bones, are subjected to multiple (combined) loads simultaneously and the resulting stresses within the material are compounded among these loads. For example, when a bone is subjected to bending and compressive loads simultaneously, the compressive stress within the bone will be equal to the sum of the compressive stresses caused by the compressive load and those resulting from the bending load.

For many materials, a linear relationship exists between stress and strain up to a certain stress level (Figure 5). These materials, which include most metals and ceramics, exhibit mechanical behavior that is ‘linear elastic’, and the ratio between stress and strain in this linear region, i.e., the slope of the stress-strain curve, is a constant. In tension and compression, this constant is a material property called the elastic modulus (E). Elastic modulus is a constant that describes a material's stiffness, i.e., its ability to resist elastic (recoverable) deformation under load. Materials with a high elastic modulus such as steels deform little, whereas materials with a low modulus such as cork or wood deform much more under a given load.

Strictly speaking, bone is not a linear elastic material because its elastic modulus is affected by temperature and strain rate, i.e., how fast it is deformed. Nonetheless, it is often appropriate to assume that the material behavior of bone is linear elastic at a specific strain rate and temperature, such as physiological body temperature.

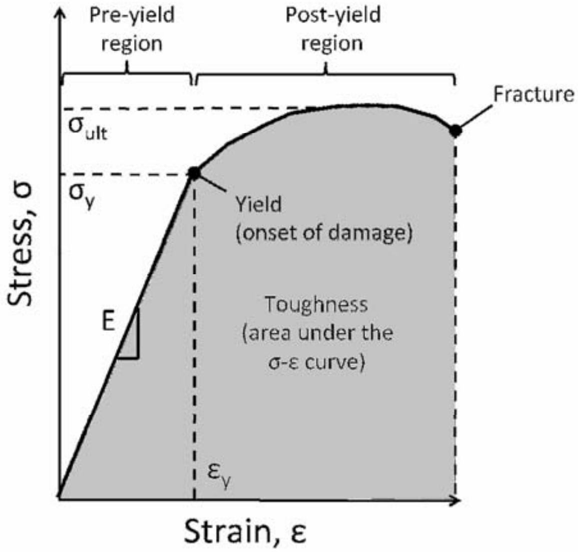

Figure 5. Tensile properties for a material exhibiting linear elastic behavior: Elastic modulus (E), yield strength (σ_y), yield strain (ε_y), and ultimate strength (σ_{ult}).

Above a certain stress level, the relationship between stress and strain in a linear elastic material ceases to be linear (Figure 5). These threshold stress and strain values define material properties called yield strength (σ_y) and yield strain (ε_y), respectively. If the applied stress or strain exceeds this threshold, irreversible damage occurs within the material. In bone, damage first occurs through the formation of microscopic cracks. Propagation of these microscopic cracks is hindered, to a certain degree, by heterogeneities in the bone microstructure. The ultimate strength (σ_{ult}) is the maximum stress that a material can carry before final fracture. In bone, final fracture occurs when a larger crack propagates across the whole bone or specimen. The amount of energy per unit volume required to fracture the bone is referred to as toughness, and it can be estimated as the area under the stress-strain curve. Thus, toughness of a material is proportional to not only its ultimate strength, but it is also largely affected by how much strain occurs within the material within the post-yield region. For example, diamond is a very strong material, but it has very low toughness because it does not undergo any post-yield strain. A summary of key terms pertinent to mechanics of materials and their definition are presented in Table 1.

Table 1. Basic mechanics of materials terminology.

Term	Definition
Stress (σ)	Measure of internal force (per unit area) acting within a deformable body.
Strain (ε)	Normalized measure of a deformable body's internal deformation, i.e., change in size, under an applied force.
Elastic deformation	Deformation that is recoverable after the applied force is removed.
Yield	Onset of irrecoverable deformation.
Elastic modulus (E)	Material property describing the ability to resist elastic deformation under load.
Yield strength (σ_y)	Material property that describes the stress required to cause the onset of permanent deformation, i.e., stress value below which deformation is recoverable.
Yield stain (ε_y)	Material property that describes the maximum internal deformation that is fully recoverable.
Ultimate strength (σ_{ult})	Material property describes the stress required to cause fracture.
Toughness	Measure of a material's resistance to fracture; energy absorbed by the material up to the point of fracture.
Hardness	Measure of a material's resistance to deformation by indentation and scratching.

For many materials such as metals, the properties are the same in all directions. These materials are described as having isotropic behavior. Bone, however, is not an isotropic material. Its microstructure has preferential orientations, which result in anisotropic (directionally dependent) properties. In the shafts of long bones, elastic modulus and strength are higher along the length of the bone (longitudinally), than in the plane transverse to the long bone axis. Typical values reported for the longitudinal tensile elastic modulus of adult human cortical bone range from 16 to 18 GPa in the femur and from 19 to 29 GPa in the tibia.[3-5] In the plane transverse to the long bone axis, modulus typically ranges from 9 to 14 GPa in adult cortical bone.[4]

MATERIAL BEHAVIOR OF BONE IN OI

Fundamental abnormalities in collagen biochemistry and bone mineralization have been measured in OI. Studies have reported that the diameters of type I collagen fibrils differ from typical bone in OI, although there have been conflicting observations as to whether the fibrils were thinner or thicker than normal.[6,7] Bone mineral crystals are also affected, since the folding and spacing of collagen influences hydroxyapatite deposition. Crystal size tends to be smaller than in typical bone, and this size appears to be affected by OI severity.[8,9] The mineral crystals do not conform to a normal plate-like shape, and they appear to be poorly organized relative to the collagen fibrils.[8] Bone mineralization density in OI is usually higher than in typical bone,[2,10,11] and is even higher in individuals with OI type III than in those with type I.[10] Finally, the calcium-phosphate ratio tends to be lower in OI bone than in typical bone.[12]

These abnormalities in collagen and mineral crystals suggest that bone material properties are compromised in individuals with OI. Little data, however, is available to describe these properties; therefore the effects of this disorder on the intrinsic properties of bones are currently not well understood. The present section offers a summary of studies pertaining to bone material properties in OI.

Mouse Models

Mouse models have been used to study how OI affects the mechanics of bones. While the material properties of mouse bones differ from those of human bones, mouse models of OI have indicated that bone properties are affected by OI. For example, *Mov13* mice, which bear similarities to mild OI in humans, have lower cortical bone elastic modulus, yield strength, yield strain, and ultimate strength than wild-type controls.[13] A mouse model of severe OI, the *oim/oim* mouse, has lower ultimate cortical bone strength and toughness, but tends to have a higher elastic modulus than their wild-type littermates.[14-17] Another model, the *Brtl* mouse for OI type IV, was found to exhibit bone material properties that vary with age.[18] Little data, however, is yet available to confirm whether these trends in bone material properties hold true for humans with this disorder.

Nanoindentation

A few studies have used nanoindentation to characterize bone material properties in biopsy and osteotomy specimens from children with OI.[11,19-21] In nanoindentation tests, a sharp indenter is pressed into the surface of a specimen creating a very small indent, and two material properties are determined from the load-displacement data: elastic modulus and hardness, a property representing the material's resistance to deformation by indentation or scratching.

In preparation for nanoindentation tests, bone specimens are dehydrated using ethanol solutions, embedded in a polymer, and their surface is polished. During the test, a diamond-tip indenter is pressed into the polished surface, creating an indentation a few hundred nanometers deep. Force and displacement are measured during the indentation, and this data is used to calculate local elastic modulus and hardness.

Because of its small scale, nanoindentation lends itself well to the testing of small specimens such as biopsies and osteotomies. Use of this technique to characterize bone tissue, nonetheless, has limitations. This test provides an estimate of elastic modulus at the site of indentation. Local elastic modulus varies within different regions of the bone microstructure.[22-24] These values further do not take into account vascular pores, which result in lower average elastic modulus at larger scales. Calculation of elastic modulus from nanoindentation involves the assumption that the specimen has isotropic properties, which, as discussed earlier, is not quite true for bone. Assumptions must also be made regarding the specimen's Poisson's ratio[†], a property that can vary both between and within bone specimens. Moreover, several experimental factors have been shown to affect the properties measured by nanoindentation in bone specimens. Therefore, bone

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[†] When a deformable body is subjected to axial tension, it tends to contract in the directions perpendicular to the load. Similarly, when it is compressed, it tends to expand in the directions perpendicular to the applied compressive load. Poisson's ratio is a material property describing the ratio of the strain occurring perpendicularly to the applied load to that occurring in the direction of the load. For bone, Poisson's ratio ranges between 0.2 and 0.6. Since bone is a heterogenous and anisotropic material, Poisson's ratio is likely to exhibit local and directional variations.

properties obtained with this technique should not be interpreted as absolute values. Nonetheless, nanoindentation provides a valuable means of comparing modulus and hardness between groups of specimens.

Results of published nanoindentation studies in OI bone are summarized in Tables 2 and 3. At the nanoindentation scale (submicrostructural scale), elastic modulus and hardness at were found to be higher in children with severe OI than in age-matched controls.[11] This observation is similar to those made in studies of the *oim/oim* mouse model of severe OI.[15-17] No significant differences were seen between OI types III and IV.[20,21] However, bone elastic modulus was found to be slightly higher in children with OI type I than in those with type III,[22] indicating that bone modulus is also higher in mild OI than in normal bone. This observation diverges from the study of *Mov13* mouse model for mild OI, in which these mice were found to have lower bone modulus than wild-type controls.[13]

Interestingly, no significant difference in elastic modulus was found by nanoindentation between the longitudinal and transverse directions in specimens from children with severe OI.[11,19] This observation is in sharp contrast to normal tissue, where modulus measured by nanoindentation is approximately 40% lower in the transverse vs. longitudinal direction.[25-27] This observation has led to speculation that OI bone material properties may not display as much anisotropy than typical bone, at least at the submicrostructural scale.

Effect of Age

Bone material behavior varies as a person ages. In typical tissue, pediatric bones are more flexible and have lower elastic modulus and strength, but higher strain to failure and toughness than do adult bones.[28] Age, however, was not found to be a predicting factor for elastic modulus and hardness in nanoindentation studies of bone specimens from children with OI.[20,22] Nonetheless, no data is yet available to describe bone material properties in adults with OI.

Table 2. Published results for intrinsic elastic modulus (E) in OI bone tissue. Results in GPa. Means (SD).

Study	OI Type	Cortical	Trabecular	Observations
[19]	III	L: 15.2 (1.9)[a]	13.6 (3.4)	No difference between L and T directions.
		T: 13.9 (2.8) [a]		No significant difference between cortical and trabecular regions.
[11]	Controls	18.8 (1.1)		E was higher in OI type III than in controls.
	III, before pamidronate	21.3 (1.5)		E did not change after 2-3 years of pamidronate treatment.
	III, after pamidronate	22.1 (2.0)		
[21]	III	19.7 (2.8)[b]	19.2 (2.0)[b]	No significant difference between OI types III and IV.
	IV	19.2 (2.4)[b]	18.2 (2.8)[b]	
[22]	I	I: 17.7 (1.8)[c]		E was slightly higher in OI type I than in type III.
		H: 16.1 (1.1)[c]		E was greater in interstitial regions than within secondary osteons.
	III	I: 17.3 (1.3)[c]		
		H: 15.2 (0.9)[c]		

a: L and T denote modulus along the longitudinal axis of the bone and in the transverse plane, respectively.

b: The authors did not indicate whether the values in parentheses represent standard deviation or standard error.

c: I and H denote results from interstitial and Haversian bone regions, respectively.

Table 3. Published results for bone hardness (H) in OI. Results in GPa. Means (SD).

Study	OI Type	Cortical	Trabecular	Observations
[19]	III	L: 0.42 (0.04)[a]	0.42 (0.06)	No difference in between L and T directions.
		T: 0.42 (0.05)[a]		No difference between cortical and trabecular regions.
[11]	Controls	0.67 (0.05)		H was higher in OI type III than in age-matched controls.
	III, before pamidronate	0.81 (0.08)		H did not change after 2-3 years of pamidronate treatment.
	III, after pamidronate	0.83 (0.11)		
[21]	III	0.70 (0.17)[b]	0.65 (0.12)[b]	No significant difference was found between OI types III and IV.
	IV	0.66 (0.13)[b]	0.62 (0.14)[b]	
[22]	I	I: 0.59 (0.05)[c]		H was slightly higher in OI type I than in type III.
		H: 0.59 (0.08)[c]		Greater in interstitial regions than within Haversian bone.
	III	I: 0.61 (0.04)[c]		
		H: 0.54 (0.05)[c]		

a: L and T denote modulus along the longitudinal axis of the bone and in the transverse plane, respectively.

b: The authors did not indicate whether the values in parentheses represent standard deviation or standard error.

c: I and H denote results from interstitial and Haversian bone regions, respectively.

Bisphosphonate Effect

Bisphosphonate treatments have become common as a means to reduce fracture risk in children with OI. It was found that elastic modulus and hardness as measured by nanoindentation were not significantly affected after two to three years of bisphosphonate treatments.[11] Similarly, in another nanoindentation study, no significant association was observed between these two properties and whether or not the subject had a history of bisphosphonate treatments prior to specimen donation.[29] It should be emphasized, however, that these studies did not measure bone material strength or toughness. Therefore, we caution that it should not be concluded, based on those results, that bisphosphonate treatments have no effect on bone material properties. By inhibiting osteoclasts, bisphosphonates influence the bone remodeling process, which may adversely affect the material strength and toughness of the bone tissue. Nevertheless, as suggested by Weber et al.,[11] the reduction in fracture incidence after pamidronate treatment is likely to be attributed to an increased bone mass and volume rather than to changes in bone material properties.

Ongoing Work

Fracture risk can be assessed by calculating stress and strain distributions within a loaded structure and comparing these results to threshold values. As discussed earlier, onset of damage in a linear elastic material occurs when the applied local stresses exceeds the yield strength, and final fracture occurs when the stress reaches the ultimate strength. While the yield strength, ultimate strength and toughness of typical human bones have been studied using cadaveric bone specimens, little data is yet available to describe these properties in individuals with OI. An ongoing study at Shriners Hospital–Chicago and Marquette University is focused on characterization of cortical bone material properties in children with OI. In this study, small bone specimens are collected during routine corrective osteotomy surgeries. Although their limited size renders them unsuitable for most mechanical test protocols, in which specimens are typically a few centimeters long, a small-scale three-point bending test methodology (Figure 6) has recently been developed and validated to characterize these small bone specimens.[30] Preliminary results indicate that, much like typical bones tissue, OI bones exhibits clear anisotropic material properties,[31] although their properties appear to differ from those of normal bone tissue. Specifically, bone material strength and elastic modulus results in specimens from children with OI[30,32] were lower than values for typical pediatric bones.[33] Further research is warranted to investigate how these properties are affected by factors such as: age, genotype, level of mobility, and bisphosphonate treatments. Finally, comparing the strength and toughness of bone tissues from individuals with and without OI would help to further our understanding of the mechanical basis of bone fragility associated with this disorder.

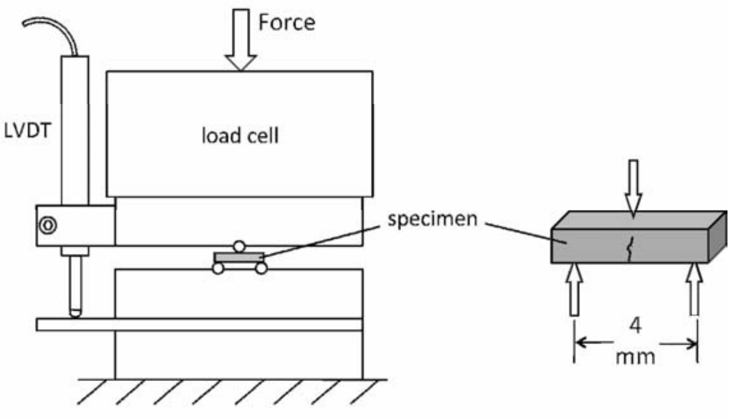

Figure 6. Three-point bending test configuration for characterization of the flexural properties of small bone specimens. A compressive force is applied with a materials testing machine bending the specimen to the point of fracture. Deflection of the specimen is measured with a linear variable differential transformer (LVDT). Bending strength is calculated from the force and deflection data.

Fracture toughness, a measure of resistance to crack growth within a material, has not yet been measured in OI bone. Future studies characterizing bone fracture toughness in OI would be valuable in understanding how this disorder affects the ability of the bone material to resist fracture propagation.

Trabecular bone is a porous structure and its effective macroscopic properties are affected by its porosity. The effective modulus and effective strength of trabecular bone both decrease with an increase in porosity.[34] While the intrinsic properties of individual trabeculae reflect the quality of the bone material itself, effective properties better reflect the capacity of trabecular bone as a structure to carry loads. Although no data is yet available to describe the effective modulus and strength of trabecular bone in OI, these values are likely to increase with bisphosphonate treatment as a result of increased trabecular bone mass. Future work to characterize the effective properties of trabecular bone in OI would be useful in structural analyses aiming to predict fractures.

CONCLUSION

The structural strength of bones, i.e., their ability to bear loads without fracturing, depends on their structure (i.e., size and geometry) as well as on the material properties of the bone tissue itself. In OI, bone structure is affected: individuals with OI tend to have small, narrow bones and low bone mass, and this is especially true in moderately severe and severe OI. Significant bowing of long bone shafts is also common in individuals with moderately severe and severe OI. These structural abnormalities can contribute to the increased fracture risk by increasing local stress levels within the bone material under a given load. The decreased incidence of fractures observed following bisphosphonate treatments in individuals with OI is likely attributed to the resulting increase in bone mass rather than to changes in material properties of the bone tissue. Although little data is yet available to describe bone material properties in humans with OI, murine models of this disorder have indicated that bone material properties are indeed compromised. Nanoindentation studies of pediatric OI bone specimens have indicated that elastic modulus tends to be increased at the microstructural scale. Conversely, preliminary findings from three-point bending characterization of surgical pediatric bone specimens indicate that bone material strength and elastic modulus at the mesoscale are lower than normal in children with OI. Finally, further research is necessary toward understanding the effects of several parameters such as age, genotype, level of mobility, gender, anatomic site, and bisphosphonate treatments on bone strength.

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ABBREVIATIONS

A	Specimen cross-sectional area
F	Force applied
L	Longitudinal direction, i.e., along the long bone axis
$L_{initial}$	Initial gage length of specimen
L_{final}	Final gage length of specimen
OI	Osteogenesis imperfecta
T	Transverse direction, i.e., transverse to the long bone axis
ε	Strain
ε_y	Yield strain
σ	Stress
σ_{ult}	Ultimate strength
σ_y	Yield strength

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