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Multi-Scale Biomechanics of Osteoporotic Spine Fracture

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Abstract

Osteoporosis, the most common bone disorder found in the elderly, afflicts from 15 to 30% Caucasian women in US and results in an estimated 700,000 spine fractures per year. The prevalence of spine fractures in the elderly is high, ranging from 20 to 50%. Fractures are biomechanical events resulting from the load applied to a bone exceeding its ability to bear load. Osteoporotic spine fracture occurs owing to diminished vertebral microarchitecture and microfailure of bone tissues, ultimately leading to a compromised whole vertebral strength, and therefore, it is a multi-scale biomechanics event. In this chapter, insights into the micromechanics of the human vertebral body gained by micro-computed tomography (CT) and micro-finite element modeling will be reviewed. Following that, noninvasive assessment of vertebral strength using quantitative CT-based finite element analysis at a continuum level and its potential applications in improving spine fracture risk prediction in the clinic will be discussed.

Keywords: osteoporosis, vertebral fracture, micromechanics, computed tomography (CT), finite element analysis, bone strength

1. Introduction

1.1 Osteoporosis and osteoporotic spine fracture

Osteoporosis is a metabolic disease characterized by an imbalance in bone formation and resorption that results in accelerated bone loss and deterioration of bone microarchitecture. This low bone mass and deteriorated microarchitecture cause a reduction in bone strength and an increased risk of fracture. Osteoporosis is the most common bone disorder found in the elderly [1]. The vertebral body and femur are common locations for osteoporosis-related fractures.

Osteoporosis results in an estimated 700,000 spine fractures per year. The prevalence of vertebral fractures in the elderly ranges from 20 to 50% with the higher prevalence in older age groups [2]. Women are more affected than men, although at least one study has reported equal prevalence of vertebral fractures in women and men [3]. Reports from the European vertebral osteoporosis study suggest that the prevalence of vertebral fractures in men is 21% at age 60–64 and increases to 29.1% at age 75–79 [4], an increase in prevalence of fracture of about 70% per decade, the same as is found in women. A National Osteoporosis Foundation expert panel estimated that 90% of vertebral fractures in white men were attributable to osteoporosis, as compared to 75% in men of other ethnic

groups [5]. Thus, age-related vertebral fractures are widespread for both sexes, and as the size of the aging population continues to increase, their incidence is expected to increase.

In particular, by the year 2050, there will be nearly five times as many people over 85 in the US as there were in 1980 and 22% of the population will be over 65 compared to only 4% in 1900 [6]. These demographic trends make the need to reduce morbidity among elderly men and women an urgent priority. The problem is also a global one. Worldwide, osteoporotic fractures are expected to increase greatly, and the associated costs may have a devastating effect on the under-funded healthcare systems of many countries [1].

Given the clinical importance of osteoporosis, it is critical to accurately identify individuals who are at risk of fracture so that treatments can be taken to prevent fractures. According to the World Health Organization (WHO) standard, osteoporosis is presently identified by bone mineral density (BMD) measurement by dual energy X-ray absorptiometry (DXA). An individual is diagnosed as osteoporosis when his/her DXA-measured t-score is less than 2.5 standard deviations of that for young women [7]. The problem is that DXA works less successfully for predicting vertebral fractures [8]. BMD alone has difficulties distinguishing between patients with and without vertebral fractures. A previous study showed that, based on DXA measured t-scores, only 44% of women and 21% of men who had nonvertebral osteoporotic fractures were diagnosed as osteoporosis [9]. This observation suggests that more than half of those individuals who eventually experience fractures are not identified as osteoporotic based on BMD measurement. These high-risk individuals often do not get drug treatments, which can effectively reduce the risk of fracture. These results have indicated the need to develop the means of assessing fracture risk beyond the bone mineral density.

Development of improved methods to diagnose and monitor osteoporosis is a fundamental aspect of any strategy to both prevent and treat this disease. Toward that end, one major obstacle in improving vertebral fracture risk assessment is the poorly understood nature of the biomechanical mechanisms of vertebral strength and the etiology of vertebral fractures [10, 11], since the vertebral fracture is caused by deteriorated microarchitecture and microfailure of bone tissues leading to a compromised whole vertebral strength, and it is essentially a multi-scale biomechanical event.

1.2 Functional anatomy of the vertebra

The human vertebral column is composed of 33 vertebrae, including 7 cervical vertebrae, 12 thoracic vertebrae, 5 lumbar vertebrae, 5 sacrum vertebrae, and 4 coccyx vertebrae. The vertebrae are separated by intervertebral discs. Each vertebra has four main structural components, including the trabecular centrum, the superior and inferior endplates, the surrounding cortex, and the posterior elements (e.g., neural arch). The vertebral body primarily resists compressive forces acting down along the spinal column.

The endplates transmit loads between the vertebral body and the intervertebral disc. Also, the porous endplates function as a nutrient pathway between the disc and the vertebral body. The microstructure of the endplates is more like condensed trabeculae rather than compact cortical bone [12]. The thickness of the endplates is ~0.4–0.8 mm and varies across spinal level [13]. Generally, the endplates are thinner in the center than in the periphery. At certain spinal levels, inferior endplates are thicker than the superior endplates [14]. Endplates are common regions in the vertebral body suffering from osteoporotic fractures and have been thought to be “weak-link” of the lumbar spine [10].

The cortical shell is located at the periphery of the vertebral body and surrounds the trabecular bone inside the vertebral body. Although the cortical shell is only ~0.25–0.4 mm [15] in thickness and makes up only ~10–20% of the total amount of bone tissue in the vertebral body [16], it can carry up to 75% of the axial compressive load [17]. The cortex is thickest near the endplates and thinnest in the mid-transverse region.

The trabecular bone is located in the interior of the vertebral body. Vertebral trabecular bone has a highly porous (>80% porosity) plate- and rod-like architecture, which provides a unique spatial network to take and distribute loads effectively [18]. Aging- or osteoporosis-associated deterioration of the trabecular microarchitecture can lead to a reduction in whole vertebral strength and an increase in fracture risk. Trabecular microarchitecture can be characterized by bone volume fraction (bone tissue volume/total volume) and other microarchitecture parameters (e.g., trabecular thickness, trabecular number, trabecular separation, structural model index, connectivity density, and degree of anisotropy) that refer to the structure, interconnection, and spatial organization of the trabeculae.

1.3 Biomechanics of vertebral fractures

Vertebral compression fractures can be categorized into anterior wedge fracture, biconcave fracture, and crush fracture, based on their deformities. Anterior wedge fracture is the most common type of vertebral fracture, but its etiology remains unclear. Many osteoporotic vertebral fractures occur due to nontraumatic loading conditions, whereas hip fractures are attributable to a fall in approximately 90% of all cases [19]. The nontraumatic nature of vertebral fractures makes it difficult to diagnose because they are accompanied silently by microstructure deterioration and bone tissue failure.

Vertebral fractures are mechanical events that occur when the applied load exceeds the ability of the vertebral body to withstand load (i.e., vertebral strength). Based on this simple biomechanics concept, a factor of risk relevant to fracture can be defined as applied load over vertebral bone strength [20]. If the factor of risk exceeds 1, then fractures are expected; if the factor of risk is less than 1, then the vertebral body is not expected to fracture. Apparently, the occurrence of a vertebral fracture depends on the mechanical loads acting on the vertebral body and, more importantly, the vertebral strength determined by its geometry, microarchitecture, bone tissue properties, etc.

Substantial changes of vertebra occur with aging and osteoporosis. Decreases in vertebral strength are caused primarily by the loss of bone density and deterioration in bone microarchitecture with age. One study estimated that the vertebral strength decreases by about 12% per decade from ages 25 to 85 [21]. Aging is also accompanied by the changes in the intervertebral disc, including disc degeneration. While age accounts for a large proportion of the variation in bone strength, individuals can show much stronger or weaker bones than would be predicted by their age alone. Similarly, BMD itself can account for some of the variations in bone strength but not all. At a given bone mineral density, the measured strength values for different individuals can be higher or lower than the expected value. Therefore, BMD measures cannot fully reflect bone strength that is directly related to fractures. This issue again highlights the importance of understanding vertebral fractures from a biomechanical perspective. On the one hand, we need an improved understanding of failure mechanisms of the vertebral body, particularly at a microlevel. For example, how do loads transfer from the intervertebral disc through the endplates into the trabecular and cortical bone and ultimately cause failure of vertebral microarchitecture? How does bone mechanical behavior at a tissue-level link to

whole vertebral strength. On the other hand, a better understanding of the biomechanics of vertebral fractures can guide us to develop more advanced approaches for evaluating vertebral strength in clinic and predicting fracture risk other than BMD. Section 2 will describe some insights into the micromechanics of the human vertebral body, derived from large-scale microCT-based finite element analysis. Section 3 will discuss an improved method based on a combination of biomechanics and CT scans to predict vertebral fracture risk, which has been shown potentials in clinic use.

2. Micromechanics of the human vertebral body

2.1 MicroCT-based finite element analysis

Computed tomography (CT) is an imaging procedure in which a narrow beam of X-rays is sent out from an X-ray source, penetrating through a specimen or a patient's body, and detected by multiple detectors to generate computerized cross-sectional images. Since different materials have their own attenuation properties, CT images can indicate basic structures or anatomies by different gray scale values. MicroCT is a type of high-resolution CT with voxel sizes down to several micrometers. MicroCT has been widely used to reveal in great detail the internal microstructure of bone, particularly for trabecular bone. Due to its high-resolution nature, microCT generally requires a limited dimension of the scanned specimen and has usually been used in laboratory research. However, *in vivo* high-resolution imaging techniques, such as high-resolution peripheral quantitative CT (HR-pQCT) and high-resolution magnetic resonance (MR) imaging, have been developed and used in clinical studies [22]. However, those imaging techniques have not been seen for using in human spine.

Finite element analysis is a powerful computational tool that can be used to study bone biomechanics. A “virtually real” experiment can be performed by finite element analysis. This technique has some advantages over traditional biomechanical experiments. First, the technique is noninvasive, and it can be performed parametrically. For example, the effects of boundary and loading conditions as well as material properties can be examined in a controlled and repeated manner. Second, the finite element model can provide much detailed information on stress and strain distributions within the vertebra as well as mechanical behaviors of a whole vertebra, while only the apparent-level mechanical properties can be obtained from experimental testing. The greatest benefit of finite element modeling in bone mechanics research may be achieved by combining the technique with biomechanical testing to leverage the individual strengths of each approach.

Finite element models can be generated directly from micro-CT images (e.g., 10–60 μm voxel resolution) using a voxel conversion approach, with which voxels representing bone tissue are converted to eight-node brick elements, whereas voxels representing bone marrow and other tissues are ignored. Elements are typically assigned with homogeneous and isotropic material properties. By simulating a loading condition, this model can be used to determine the apparent-level mechanical properties of the bone (e.g., stiffness and strength) as well as tissue-level stress/strain in the bone. This modeling approach can be validated by comparing predicted outcomes with experimental measures. The microCT-based finite element analysis was first used in 1995 to investigate the mechanical behavior of trabecular bone [23]. Since then, much insight has been gained into the micromechanics of trabecular bone by using microCT-based finite element analysis [24, 25]. MicroCT-based finite element modeling of the human whole vertebral body was first reported in

2004 [26]. The models of whole vertebrae typically have in the order of 300 million degrees of freedom, and thus, the analyses require substantial parallel computational power, especially when geometric and material nonlinearities are considered.

The whole vertebral finite element models implicitly capture the trabecular microarchitecture, the thin cortical shell, and the porous endplates of the vertebra. Once the general modeling approach and model parameters have been validated, the models can be used to understand the micromechanics of the vertebral body and to link the microarchitecture or tissue material property alterations with whole vertebral mechanical behavior. Also, the microCT-based finite element models can be used to elucidate the failure mechanisms in the trabecular bone, cortical shell, and endplates. All these cannot be done with conventional experiments. So far, this technique has been applied to human whole vertebral bodies to determine cortical and trabecular load sharing, locations of high-risk tissue distributions, mechanisms of vertebral endplate failure, and relationship between microarchitecture and whole vertebral mechanical behavior [16, 26, 27]. The following subsections will introduce some additional detailed findings from the author's own work based on the microCT-finite element analysis of human whole vertebrae.

2.2 Effects of compression and forward flexion on the risk of vertebral failure

Uniform compression and forward flexion are common loading conditions that our vertebral bodies experience during daily life, corresponding to upright stance and stoop postures. Despite the high prevalence of vertebral wedge fractures in the clinical population, the mechanics of these fractures are not well understood. Clearly, the morphology of wedge fractures, in which the anterior side is shortened in the order of 15% more than the posterior side, is suggestive of an important role of forward flexion. Forward flexion of the spine motion segment might increase stresses within the anterior vertebral body including the cortical shell and trabecular bone, which could further cause failures of those bone tissues. Experiments using miniature pressure transducers have measured a greater pressure in the anterior half of the intervertebral disc when the disc-vertebra-disc segment was loaded in forward flexion [28]. However, whether this flexion-induced increase in the pressure of the anterior disc would increase the tissue stresses within the underlying cortical and trabecular microstructure of the vertebra remain unclear. This is mainly due to the technical difficulty of measuring such stresses *in vivo* or *in vitro*. Finite element modeling based on high-resolution microCT images of the vertebra is well suited to address this difficulty.

To gain insight into the etiology of wedge fractures, studies have been performed to investigate the high-risk tissue distribution within the human vertebral body for both forward flexion and uniform compression loading conditions [29]. Micro-CT-based high-resolution (60 μm) finite element models of 22 human T9 vertebral bodies with compliant discs (elastic modulus = 8 MPa) were built, and linear elastic finite element analysis was performed to mimic forward flexion or uniform compression loading. The compliant disc was also replaced with a stiff polymethylmethacrylate (PMMA, elastic modulus = 2500 MPa) layer in the vertebra-disc model to mimic a cadaveric experimental case. Results demonstrated that forward flexion increased the overall compressive load on the anterior half of the intervertebral disc. The spatial distribution of the vertebral bone tissues at the highest risk of initial failure, being identified as the top 10% percent of highly stressed bone tissues of the vertebral model, was shifted slightly toward the anterior aspect of the vertebral body. Despite that, the high-risk bone tissues were located primarily within the central regions of the trabecular bone and endplates (**Figure 1**). However, when the compliant disc

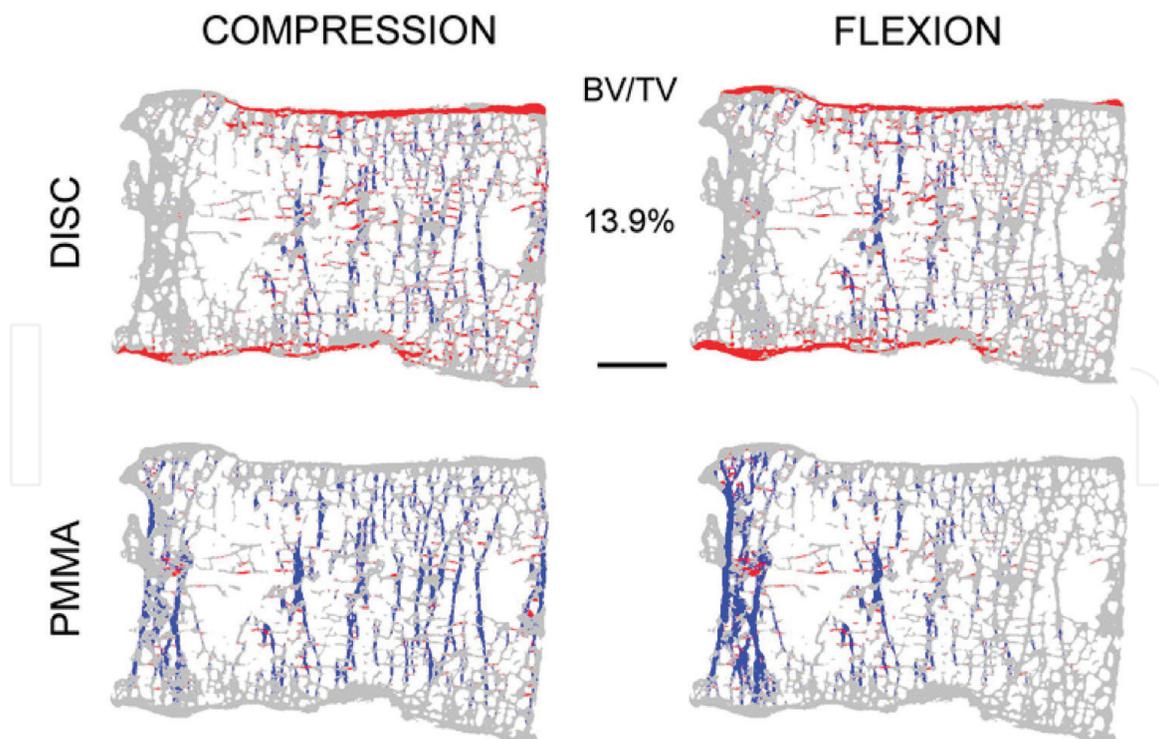


Figure 1.

The distribution of high-risk tissue at a mid-sagittal section of a vertebra with bone volume fraction (BV/TV) of 13.9%, for disc versus PMMA loading (compressive tissue-level failure is blue, and tensile tissue-level failure is red). Scale bar: 5 mm [29].

was replaced with PMMA, the anterior shift of high-risk tissue was much more appreciable. These results suggest that forward flexion loading does not appreciably change the spatial distribution of stress within the vertebral body when a compliant disc is presented adjacent to the vertebral body. The occurrence of anterior wedge fractures in cadaveric experiments in which forward bending forces were applied via a stiff material (e.g., PMMA) does not replicate the *in vivo* situation in human spine where compliant physiological discs exist.

The results from those high-resolution microCT-based finite element models indicate that the stress distribution of vertebral bone tissue, or at least the distribution of the most highly stressed bone tissues, is insensitive to applied compression versus forward flexion loading. This insensitivity could be explained by a simple beam-on-elastic-foundation model, in which the endplate and disc together behave as a “flexible” beam resting on an elastic foundation of trabecular bone [29]. Therefore, maximum stresses in the trabecular foundation occur beneath the center of the applied load. For uniform compression, the center of the applied load is in the central region of the vertebra, while for forward flexion, it is just slightly anterior to the center of the vertebral body.

The above mechanism applies to the loading of the endplates via a compliant disc but does not apply for the loading via the stiff PMMA. The PMMA and endplate together behaves like a “rigid” beam on the elastic foundation of trabecular bone. Thus, maximum stresses in the vertebral bone occur in the most anterior bone for forward flexion loading (**Figure 1**). Since PMMA may never represent any real disc in human spine anterior wedge fractures might not directly happen given a forward flexion loading. However, for the patients who undergo artificial disc replacement or spine fusion surgery, where their disc space is filled with a stiff material like PMMA, the adjacent vertebral bodies may be at an increased risk of wedge fracture when loaded even with a moderate degree of forward flexion.

2.3 Effects of the intervertebral disc on vertebral bone stress

Anterior wedge fractures are thought to be associated with forward flexion loading, under which the bone tissues in the anterior portion of the vertebral body are at the highest risk of initial failure. However, previous cadaver experiments have shown that bone failure occurs typically in the central regions of the trabecular bone and endplates of the vertebral body, regardless of uniform compression or forward flexion [30, 31]. As detailed above, high-resolution finite element modeling of the vertebral motion segment with a compliant intervertebral disc (elastic modulus = 8 MPa) has shown that the high-risk bone tissues in the vertebral bone are distributed primarily in the central regions of the trabecular bone and endplates for both compression and forward flexion loading [29]. Only when the flexion loading is applied to the vertebra through a stiff layer of PMMA (elastic modulus = 2500 MPa), most highly stressed bone tissues are located in the anterior aspect of the vertebra. These results imply that the material properties of the intervertebral disc may influence the distribution of vertebral stress. The questions are then: can typical variations in disc properties lead to an anterior wedge fracture? What is a typical range of disc material property?

It is known that alterations in the material properties and morphometry of the disc are associated with aging and degeneration [32, 33]; disc degeneration and loss of the height lead to an elevated risk of vertebral fractures [34]. However, it is unknown whether typical variations in the overall mechanical properties of a disc can affect either the location of high-risk tissues within the vertebra or the magnitude of vertebral stress.

To answer those questions, mechanical testing has been conducted on 16 individual whole discs from cadavers (66 ± 16 year old; mean \pm SD) to measure a homogenized “effective” linear elastic modulus of the entire disc [35]. The measured elastic modulus of whole discs and the disc height were then input and varied parametrically in micro-CT-based finite element models (up to 80 million elements each) of T9 human vertebrae. The vertebral models were then virtually loaded under moderate forward flexion. The changes in stress or high-risk tissue distribution were determined as a function of the effective modulus and the height of the intervertebral disc.

Across all disc specimens, the measured effective modulus of the intervertebral disc ranged from 5.8 to 42.7 MPa; the average disc height ranged from 2.9 to 9.3 mm. Based on experimental measures of whole disc modulus [35, 36], it appears that the effective modulus of human intervertebral discs does not exceed about 100 MPa.

When the disc effective modulus increased and the disc height decreased across those measured typical ranges, the vertebral bone stresses increased but their spatial distribution was largely unchanged (**Figure 2**). Most of the high-risk tissues appeared in the central trabecular bone and endplates of the vertebra. Therefore, it can be concluded that for a moderate degree of kinematically imposed forward flexion loading, typical stiffening (increasing in disc effective modulus) or narrowing (decreasing in height) of the disc can increase the overall stress level within the vertebral body but may not lead to an anterior failure of the vertebral body.

The spatial distribution of high-risk tissue within the vertebral body is insensitive to typical variations in the effective modulus or height of the adjacent intervertebral disc. This can be explained by beam-on-elastic-foundation theory. Since high anterior stress does not develop in the vertebral bone for moderate forward flexion across the range of typical disc properties, typical variations of disc properties or height may not be directly related to a wedge-shaped fracture.

The sensitivity of the stress magnitude within the vertebral body to the effective modulus and height of the disc may have clinical implications for fracture

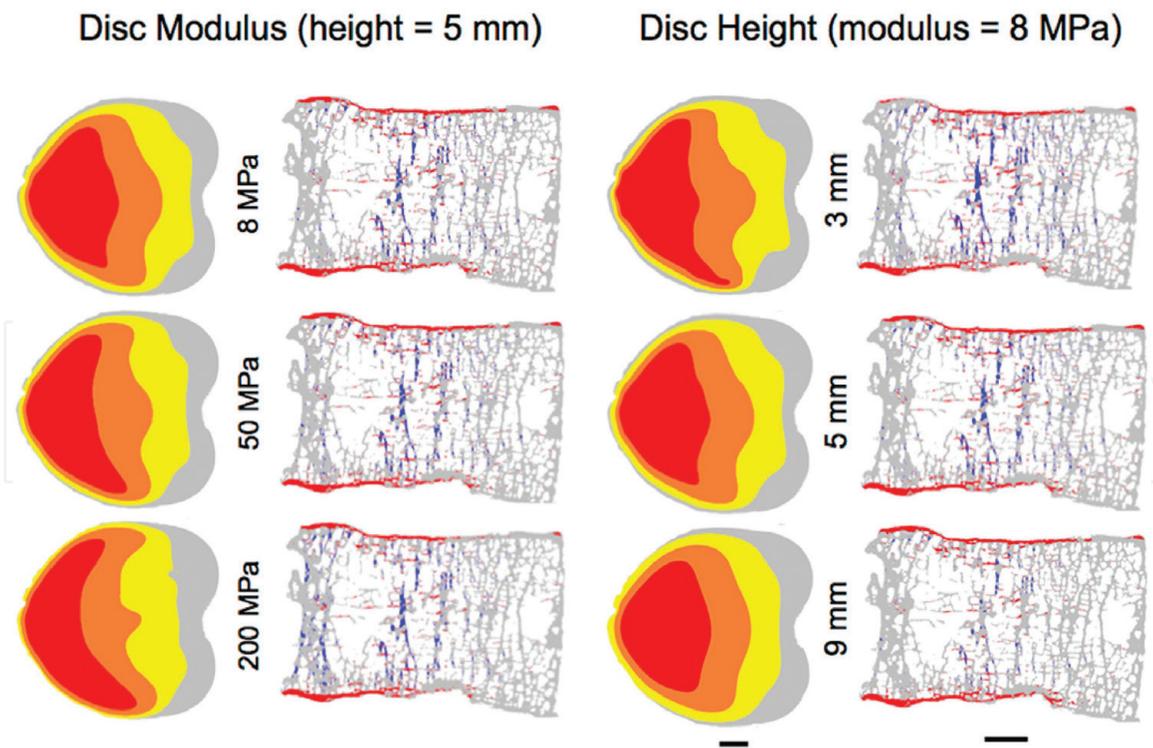


Figure 2.

Variations in the spatial distribution of axial compressive stress at a mid-transverse section of the superior disc (colors denote quartiles, red being the highest loaded, and gray the least) and the distribution of high-risk tissue at a midsagittal section of the vertebra (red and blue indicate the presence of high-risk tissue in tension and compression, respectively), for a typical range of values of the effective modulus and height of the disc. Scale bars: 5 mm [35].

risk assessment. Several studies have shown that clinical CT-based (about 1-mm resolution) finite element analysis of the human spine can predict new vertebral fractures both for women and men [37, 38] better than what DXA or quantitative CT-measured BMD can do. Those CT-based finite element analyses generally employed a compressive loading condition for all vertebrae, and loads were applied through a stiff layer of PMMA instead of a physiological disc. Since the magnitude of vertebral stress or fracture risk of vertebra is related with the material property of the disc, it can be implied that further improvements to this type of clinical finite element analysis might be needed by using actual patient-specific values of disc effective modulus. Obtaining accurate patient-specific values of disc modulus has been difficult, but this may be an area of future research as far as fracture prediction is concerned.

2.4 Possible mechanisms for spine wedge fractures

It has been shown that forward flexion loading may not directly result in an anterior wedge fracture. Aging or degeneration-related changes in disc material property and morphometry would not alter the central distribution of high-risk tissue within the vertebral body and thus may not cause wedge fractures. Therefore, the etiology of wedge fractures may lie somewhere else.

Adams [28] proposed that, with disc narrowing, habitual erect standing can lead to anterior unloading as contact occurs largely at the facet joints, and the load is transferred more through the neural arch. Such anterior unloading may cause stress shielding and adaptive bone loss of the anterior portion of the vertebral body, thus compromising the strength of the anterior bone. When a forward flexion load acts on the vertebral body, the anterior portion would fail first and thus a wedge-shaped fracture would occur.

Alternatively, it is possible that moderate forward flexion loading is not directly related with wedge fractures instead more severe forward flexion loading is. Some experiments that used a greater degree of forward flexion have found anterior wedge fractures, regardless of the state of disc degeneration [39–41].

Another possible explanation is that the modest forward bending produces initial vertebral fractures primarily in the endplates and their underlying central trabecular bone [24]. Subsequent cyclic bending loading and perhaps creep can cause progressive collapse into the anterior vertebral body. In that case, the observed morphology of the wedge-shaped fracture may reflect only the end result of the entire fracture process. It is possible that the disc may behave stiffer when its height decreases with degeneration or when the disc is loaded at a high rate, leading to increased stress within the central vertebral body, which could eventually propagate into an anterior wedge-shaped fracture. This observation could explain why degenerated-related disc space narrowing is often related with an increased risk of vertebral fractures regardless of fracture types [34].

In addition, vertebral fractures may be related to fatigue damage of bone tissues under cyclic loading [11]. Fracture might be the end of a gradual process of cumulative “fatigue failure” of the vertebral body. Or, fractures may occur slowly under constant load by gradual “creep” deformation. Clearly, further research is required to have a deeper understanding of mechanisms of spine wedge fracture.

2.5 Effects of bone tissue mechanical behavior on whole vertebral strength

The post-yield ductility of bone tissue is a type of tissue-level mechanical behavior. Bone tissue ductility is associated mainly with organic components and enables the bone tissue to deform and take load beyond the elastic range. One poorly understood multi-scale biomechanical issue is how tissue-level post-yield ductility affects the organ-level strength of the vertebral body. This multi-scale relation is also of interest clinically as tissue-level ductility can be very low in some bone pathologies, such as osteogenesis imperfecta.

This multi-scale biomechanics problem is very challenging for structurally complex vertebrae that contain both trabecular bone and cortices. It is difficult to relate any changes in tissue-level post-yield ductility to mechanical behavior (e.g., strength) of a whole vertebra. Nonlinear finite element analyses based on high resolution microCT images are well suitable to address these challenges since those large-scale finite element models can contain fine details of bone microarchitecture as well as tissue-level mechanical behaviors. Studies have been performed to investigate how whole vertebral strength is changed when the tissue-level post-yield deformation is varied from being fully ductile to fully brittle [42]. Computational simulations make it feasible to quantify the effects of tissue-level ductility on whole vertebral strength in a repeated measures manner, which is not possible only with experimentation.

For each finite element model of vertebra, two separate nonlinear finite element analyses can be performed to simulate the fully brittle and fully ductile tissue-level failure behaviors. For the fully ductile behavior, tissue-level failure is assumed by yielding; the bone tissue can only yield, it never fractures, and there is no limit on the magnitude of the post-yield tissue-level strains. For the fully brittle behavior, tissue-level fracture is assumed to occur once the yield stress (in either tension or compression) is exceeded. The elements in the computational models will be removed once they are fractured (or their yield stresses are exceeded). For all other factors, including tissue-level elastic modulus and yield stress, held fixed. For each vertebra, a finite element model can be generated (60–82 μm element size; up to 120 million elements) and virtually loaded in uniform compression. Results have shown

that changing the bone tissue behavior from fully ductile to fully brittle reduced whole vertebral strength by about 40%. At overall structural failure, there was 5–10 times less failed tissue for the fully brittle than fully ductile cases. That being said, the whole vertebra is substantially strengthened when the underlying tissue is more ductile as increased ductility enables initially yielded bone tissue to continue to support the external loads. Conversely, when the bone tissue is more brittle, many of the trabeculae stop contributing to overall load bearing as the overall structure failure quickly occurs after fracture of the initially failed tissue and the lack of alternative viable load paths. These multi-scale biomechanics studies indicate that the strength of the vertebral body is determined by both bone mass and tissue-level ductility or the extent to which the bone tissue can deform beyond the tissue-level elastic range without fracturing or developing appreciable cracking or damage.

3. Biomechanical CT-based spine fracture risk prediction

3.1 QCT-based finite element analysis

DXA scanning is the clinical standard for vertebral strength (or related fracture risk) assessment. However, DXA as an imaging modality is limited due to its two-dimensional nature and its inability to differentiate material and geometric features. Quantitative computed tomography (QCT), being three-dimensional, overcomes these limitations. However, being an imaging modality that only describes bone density and geometry, it cannot describe biomechanical properties of the vertebra, an attribute that is obviously desirable for bone strength assessment. QCT-based “voxel” finite element models of the vertebral body [43] can be generated directly from QCT scans by converting voxels of the images to hexahedron elements and can be subjected to any loading conditions. Effectively, these models integrate all the information in QCT scans in a biomechanically meaningful manner and therefore promise to overcome all limitations associated with both DXA and QCT. This is so-called “biomechanical CT”, a concept first proposed by Keaveny [44].

An endpoint clinical tool may use a strategy in which the QCT scan is converted, voxel by voxel, directly into a finite element model. This “voxel-based” finite element modeling technique uses the QCT voxel grayscale values and dimension data to automatically develop a finite element mesh for the region of interest [45]. Alternatively, smooth-meshed models with tetrahedral elements can be created [46, 47]. Finite element in the model is assigned local material properties based on the calibrated gray-scale information in the CT scan. Such material property-density relations have been shown to follow power laws and are typically derived from cadaver experiments [48]. The finite elements themselves can be hexahedron or voxels, can be tetrahedral or curved, and can employ either linear or quadratic nodal-displacement formulations; special treatment of the thin cortical shell via the use of shell elements may also be implemented. Different loading conditions typical of habitual activities or more spurious overloads can be applied depending on the clinical application. Outcomes of QCT-based finite element analysis include vertebral strength, load-strength ratio, and fracture patterns and locations. These outcomes focus on the overall structure and biomechanics of bone rather than simply bone mineral density—which is most appropriate given that a bone fracture represents a biomechanical event in which external loads applied to the bone have exceeded the strength of the bone.

Validation of the QCT-based finite element model can be done by comparing model output data with measured values in mechanical testing of cadaver vertebrae.

There are several ways to validate the accuracy of the model. For example, strains at the bone surfaces of the vertebra can be measured by strain gauges and compared with the predicted strain values of the model. Alternatively, digital image/volume correlation can be performed to measure deformations of both surface bone and internal structures of the vertebra [49]. More often, apparent-level strength and stiffness measured from cadaver tests are used for validating the finite element models.

Cadaver studies have shown that QCT-based finite element analysis provides a better estimation of vertebral strength than BMD, as measured by either DXA or QCT alone [50–55]. R^2 values for prediction of experimentally measured whole vertebral compressive strength based on QCT-finite element analysis are in a range from ~ 0.8 to 0.9 , and the slope between mechanical test-measured and finite element-predicted strength values can be very close to 1 [50–53]. However, it should be noted that QCT-based finite element analysis works well in predicting vertebral stiffness or strength for the uniform compression loading condition but has not performed as well for anterior bending [54, 55]. For example, one study found that vertebral strength in anterior bending was moderately predicted by QCT-based finite element analysis ($R^2 = 0.34\text{--}0.40$), which, however, was still better than QCT-based BMD ($R^2 = 0.14\text{--}0.22$) [54]. Another study also found moderate correlations between measured stiffness or strength and BMD ($R^2 = 0.27$ or 0.34) when the vertebrae were tested under anterior bending. Although QCT-based finite element analysis improved those stiffness or strength predictions appreciably ($R^2 = 0.49$ or 0.79), the correlations for anterior bending were not as good as those for uniform compression [55]. This may suggest different failure mechanisms of the vertebral body when loaded in uniform compression versus anterior bending. Recent studies have used microCT-based digital volume correlation to validate the accuracy of QCT-based finite element analysis in predicting vertebral failure patterns for compression and anterior flexion [49].

Currently, QCT-based finite element modeling of human vertebrae has been improved by addressing different types of loading, for example, compression and forward flexion, and the effect of intervertebral discs on vertebral strength assessment [56–58]. However, compression versus forward flexion loading has been shown to have a minor effect on vertebral stress distribution based on the observations from high-resolution microCT-based finite element analysis [29]. Variations in disc properties only affect the magnitude of the overall stress within the vertebral body, and thus, disc may serve as a critical variable that needs to be considered in the QCT-based finite element models in the future [35]. Continuing research in this field would advance the clinical use of QCT-based finite element analysis, particularly in predicting risk of osteoporotic fractures.

3.2 Vertebral fracture risk prediction based on QCT-Finite Element Analysis

Based on validation and verification with cadaver studies, QCT-based finite element analysis has been applied in clinic to predict vertebral fracture risk and evaluate osteoporosis treatment. This type of biomechanical model has been shown to improve fracture risk prediction clinically compared to what is currently possible using DXA and QCT.

The QCT-based finite element analysis was first applied to assess vertebral bone strength in live patients in a clinical research study in the early 1990s and used since then in many orthopedic biomechanics laboratory research studies [59]. There is a modest body of earlier work on finite element modeling of the vertebra that already showed great potential. In a seminal study, Faulkner et al. [59] tested the hypothesis that patient-specific bone distribution information

contained in QCT voxel-based finite element models of lumbar vertebral bodies could more accurately estimate vertebral strength than bone density alone. They built voxel-based finite element models of the vertebrae taken from QCT scans of actual patients and confirmed their hypothesis by demonstrating that the models were able to better discriminate (retrospectively) osteoporotic versus nonosteoporotic patients. Further, they presented evidence that the finite element modeling technique has more discriminatory power at fracture risk assessment than measures of BMD. Bozic et al. [60] studied the effects of axial compressive loading on cervical vertebrae using a voxel-based finite element model. The model mechanistically confirmed the fracture initiation site and patterns found in clinical burst fractures of cervical vertebrae. Homminga et al. [26] used voxel-based models to study differences in the load distributions between healthy versus osteoporotic vertebrae. They showed that there was about 16% of the trabecular bone at risk of fracture in osteoporotic vertebrae versus about 1% in healthy vertebrae. Since then, many studies have demonstrated that bone strength derived from QCT-based finite element model is able to discriminate osteoporotic versus nonosteoporotic patients more effectively than BMD derived from DXA and QCT [61–63]. More importantly, QCT finite element models can predict new clinical vertebral fractures in both men and women better than DXA or QCT alone [37, 38, 64, 65]. This technique has shown a great potential in clinical application for fracture risk prediction of both spine and hip osteoporotic fractures and it is currently in clinical trials in US.

4. Conclusion

Osteoporotic spine fracture is a global issue affecting a great percentage of population, especially for the elderly. Since fracture is a biomechanical event, a better understanding of the multi-scale biomechanics of the osteoporotic spine fracture would help develop better tools to improve fracture risk prediction and eventually prevent osteoporotic fractures. With the advent of micro-CT finite element modeling, studies have been performed to reveal the mechanisms of tissue deformation and microstructural failure within the entire vertebral body, information that provides insights into the micromechanics of the human vertebral body. While DXA works quite well for the hip at fracture risk prediction, it is far less successful for the spine and there is a need for improvement. The QCT-based finite element analysis promises such improvement since it is now possible to develop high-fidelity finite element models, clinically, on a patient-specific basis.

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Conflict of interest

The author has no conflict of interest to declare.

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