It is estimated that more than 2 million people experience fractures attributable to osteoporosis every year in the United States. Although much of the mortality and morbidity due to osteoporosis-related fractures are associated with those of the hip, pain and disability associated with fracture of the spine is no less of a problem, especially when the fact that 50% of the elderly female population is expected to have at least one vertebral fracture is considered. Thoracic 12 and lumbar 1 together have the highest incidence of vertebral collapse and account for 24.2-60.6% of all vertebral fractures among T3 to L5 levels. Overall, the junction of the thoracic and lumbar spine (T12-L1 vertebrae) is a critical site as far as vertebral fractures are concerned. It is clear that low bone density is associated with reduced bone strength and increased risk of fracture, however, it is also clear that prediction of fracture risk and bone strength from bone mineral density (BMD) alone can be problematic. The role of bone quality, encompassing parameters other than those represented by bone mass, appears important. However, little is known about which specific parameters may be at play. One such factor, the variability of tissue properties within a bone, may be at least as important as the average quality of the tissue in determining fracture risk. The general hypothesis of this research has been that the microarchitecture and functional mechanical properties of bone can be regulated by controlling statistical measures of local stresses/strains (i.e., the magnitude and variability of an appropriate stress measure within the tissue). In support of this hypothesis, we have shown, using microcomputed tomography imaging, large-scale finite element modeling and mechanical testing, that the variability (coefficient of variation) of trabecular von Mises stresses in human vertebral cancellous bone increases with decreasing strength and with increasing levels of in vivo microdamage. We have also found that cancellous bone from the T12 and L1 vertebrae is structured to have higher trabecular von Mises stress variability in females than in males for a given level of average trabecular stress; a potentially important difference between females and males that could not be explained by conventional microarchitectural measures.