Journal of Bone & Mineral Research (IF:6.314)
February 2018
Department of Orthopedics and Traumatology, The University of Hong Kong

Subchondral Trabecular Rod Loss and Plate Thickening in the Development of Osteoarthritis

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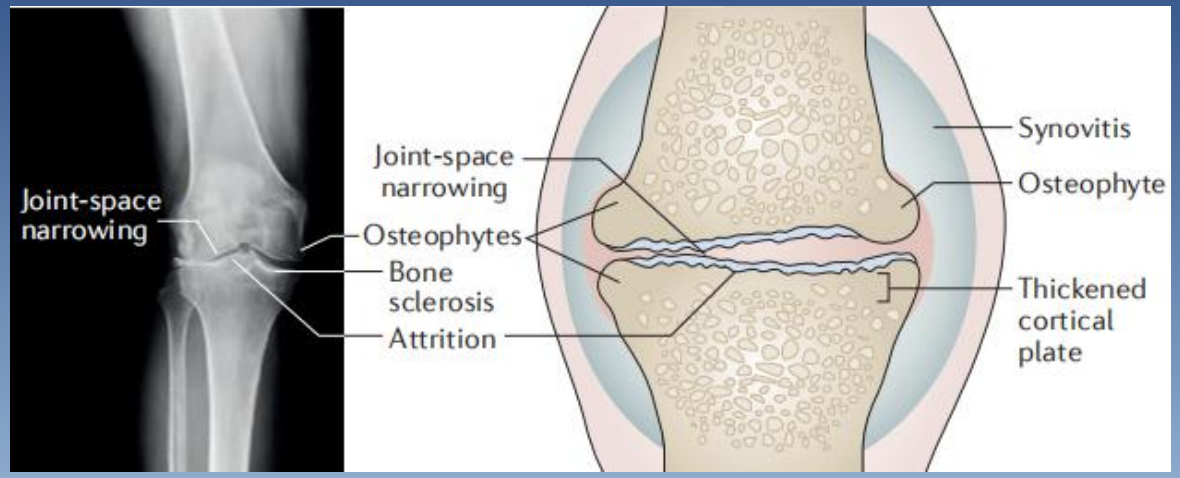
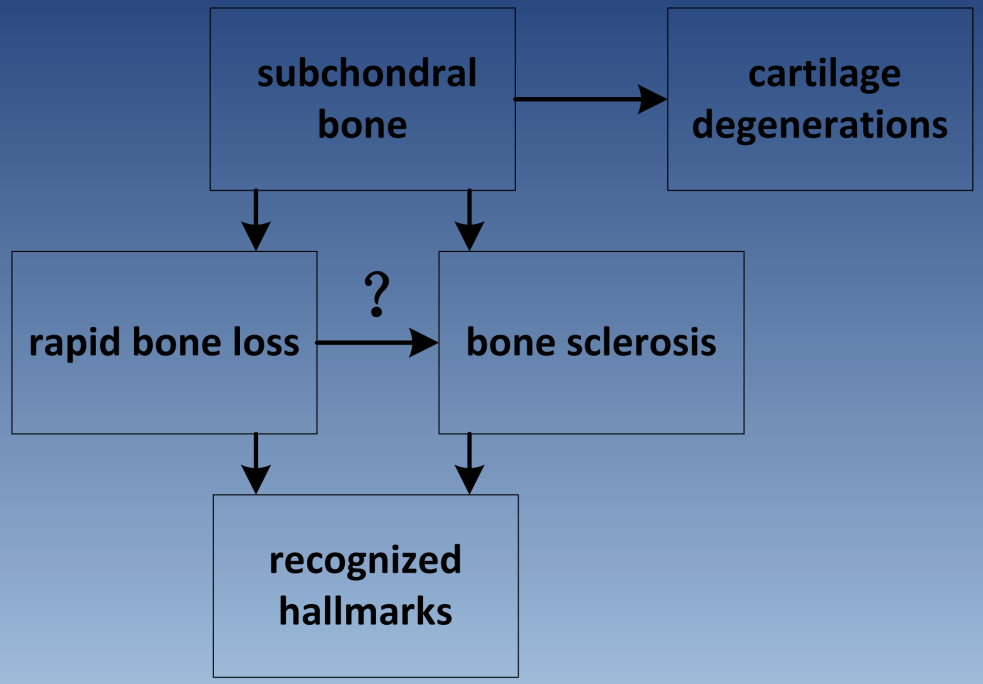
Date:March 27, 2019

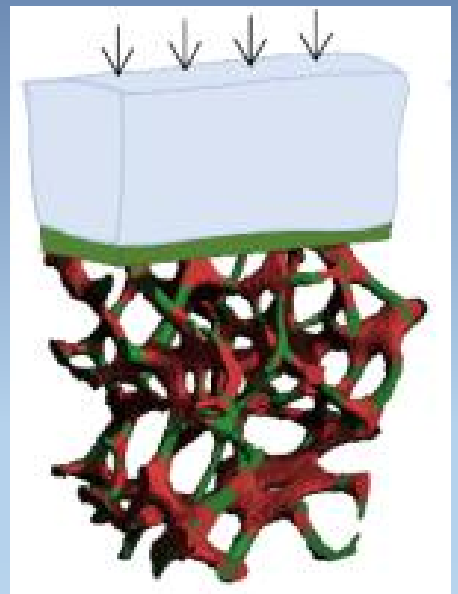
Introduction



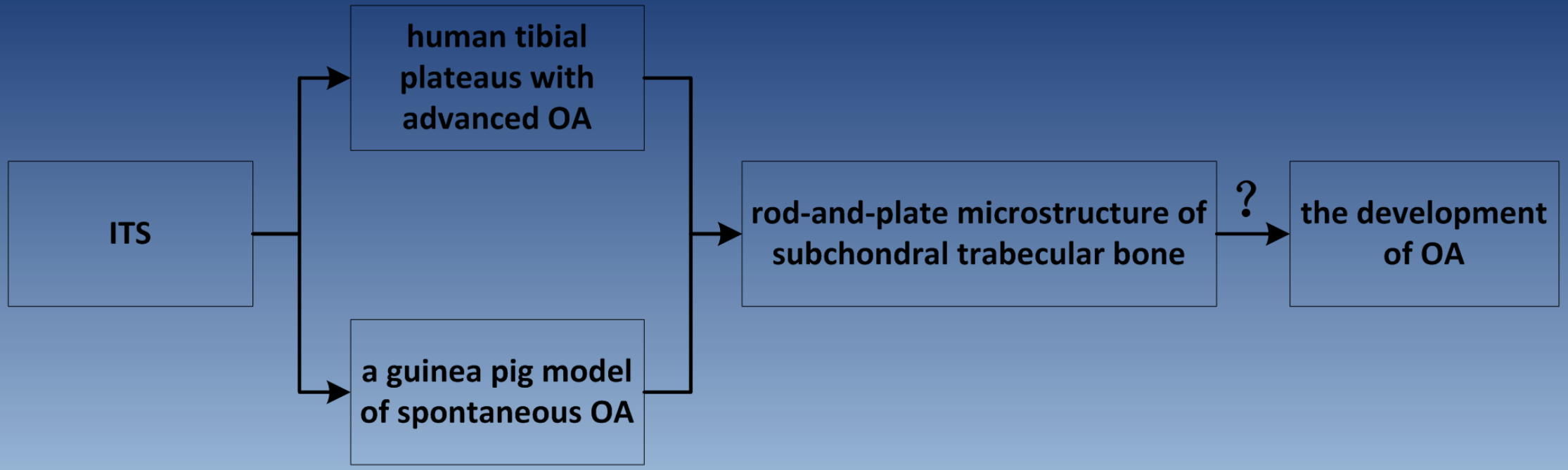


OA involves pathologies in multiple tissues within the joint, including the articular cartilage, subchondral bone and the synovium. **The sequence by which these abnormalities develop and how they contribute to disease initiation and progression remains under debate**. In the subchondral bone, rapid bone loss following traumatic injuries, a major risk factor for OA, and bone sclerosis at advanced stages of the disease are well recognized hallmarks in both animal and human OA. Alterations in the subchondral bone have been shown to predict or precede severe cartilage degenerations. **However, how abnormal bone resorption eventually lead to bone sclerosis remains unexplained.**

This may be due to limitations in the current outcome measures for subchondral bone and insensitive to more subtle changes. The application of more advanced image-based analytical techniques may be necessary.



Microscopically, healthy trabecular bone consists of an intricate network of rod-like and plate-like trabeculae, which undergoes dynamic bone remodeling to maintain its microstructural and mechanical integrity. Previously, our group developed a novel 3D microstructural analysis technique, Individual Trabecula Segmentation (ITS), which decomposes the trabecular network into individual rods and plates while rigorously preserving the original topology and biomechanical properties.



In this study, we used ITS to examine the rod-and-plate microstructure of subchondral trabecular bone, in conjunction to changes in the subchondral plate and overlying cartilage, in human tibial plateaus with advanced OA and in a guinea pig model of spontaneous OA. We aim to investigate the role of subchondral trabecular and plate changes in the development of osteoarthritis

Methods

1.Human Study

Advanced knee OA patients

Healthy human knee

(1) μCT (ITS analyses)

(2) Histology： Safranin O/Fast Green staining

2.Animal Study

Female Dunkin Hartley guinea pigs : euthanized at 1 、 2、 3 months

Female Bristol Strain 2 type guinea pigs : euthanized at 1 、 2、 3 months

(1) μCT (ITS analyses)

(2) Histology： Safranin O/Fast Green staining

Results

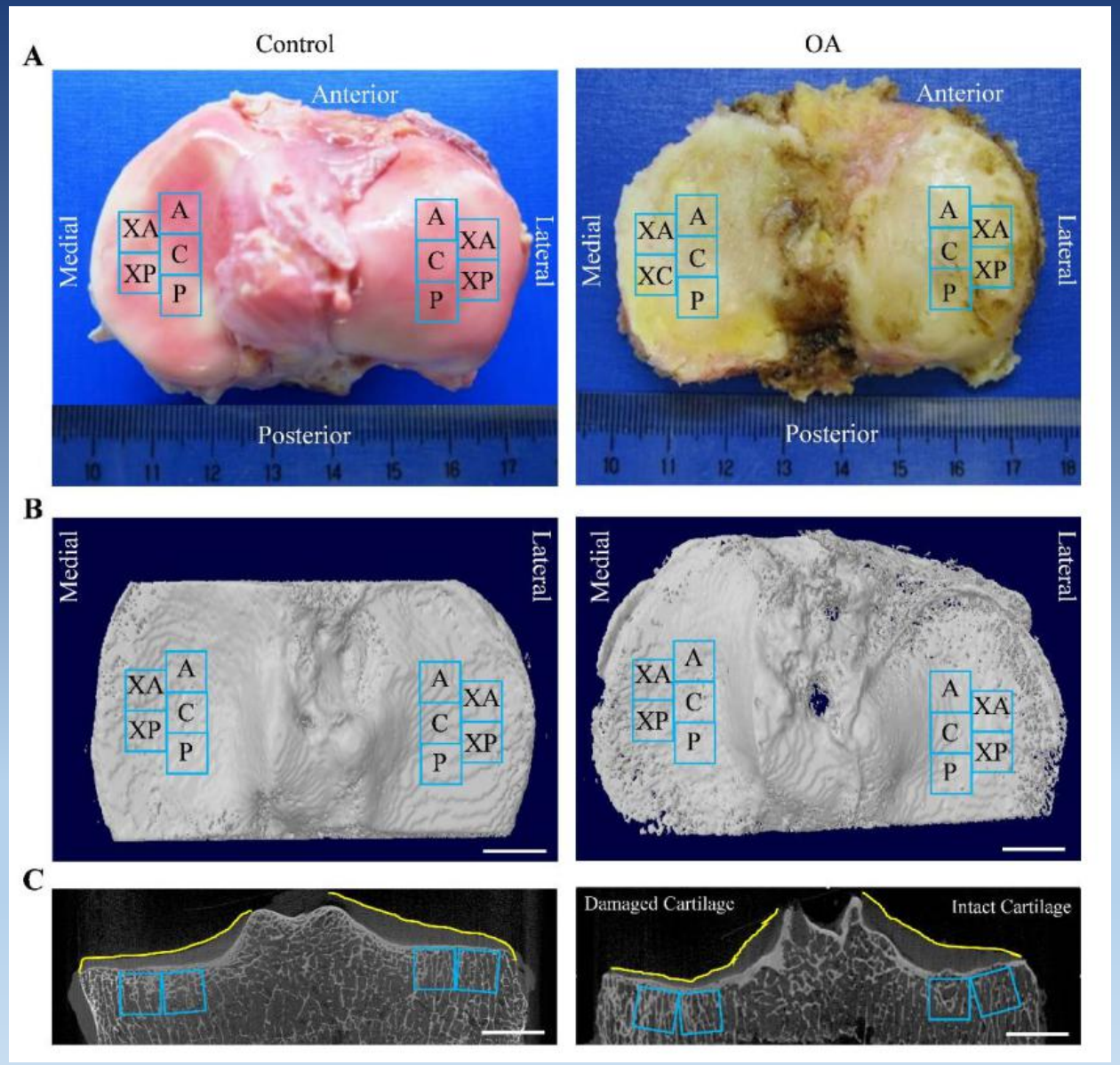


Figure 1. Macroscopic view (A), reconstructed top view (B) and coronal slice (C) from µCT scanning of control (n = 11) and OA (n = 78) tibial plateaus. The squares indicate the selection of region of interests (ROIs) of cartilage and subchondral bone for subregions (anterior, central, posterior, external anterior, and external posterior) from both medial and lateral condyles. The yellow lines in C indicate the border of cartilage visualized from µCT scan. Scale bars represent 10 mm.

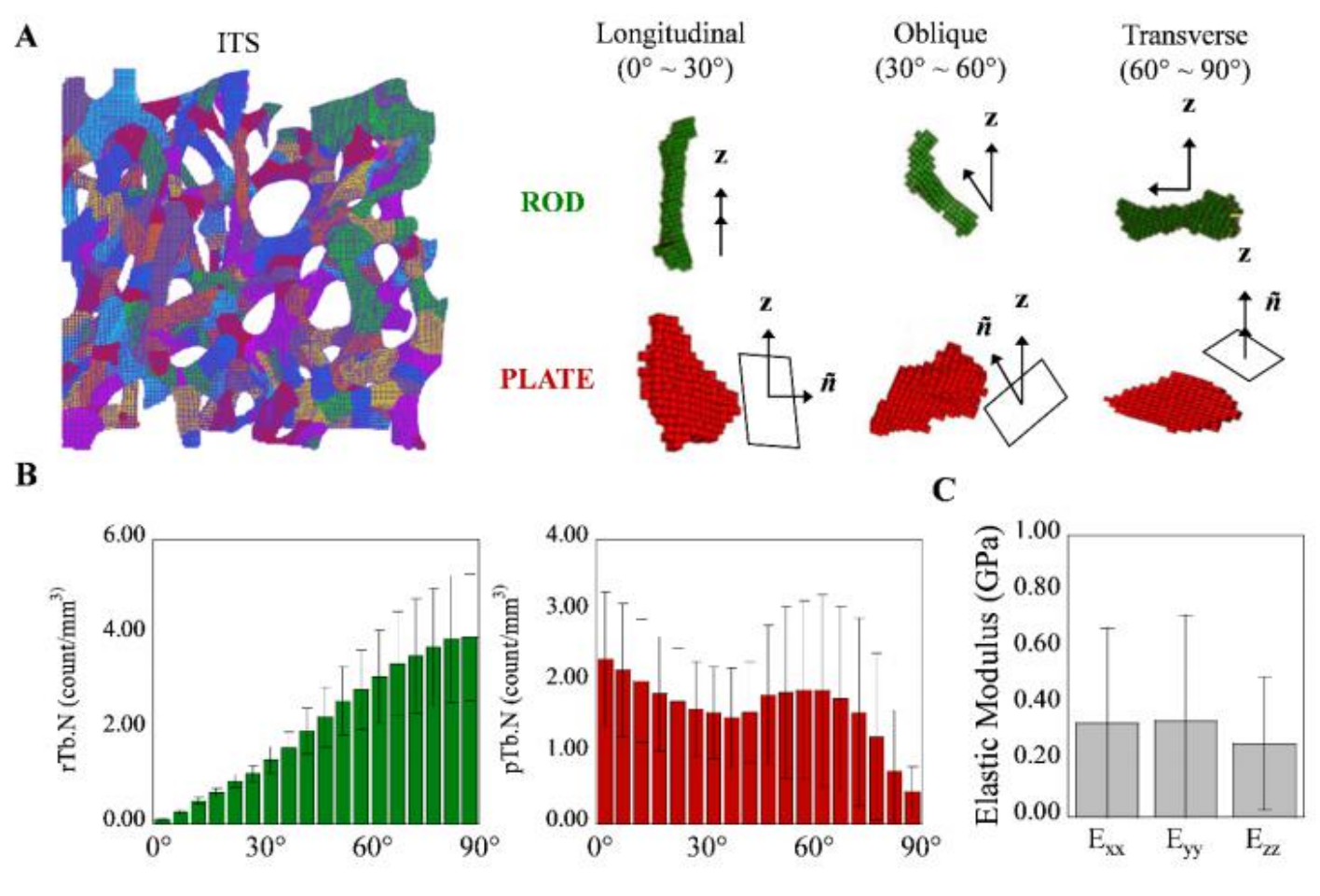


Figure 2. Rod-and-plate configuration in the healthy subchondral trabecular bone.
(A) Subchondral trabecular bone immediately beneath the subchondral plate were subjected to ITS analyses, decomposed into individual rod (labeled in green) and plate (labeled in red).
(B) Orientation distribution of trabecular rods and plates in healthy subchondral trabecular bone.
(C) Elastic modulus of healthy subchondral trabecular bone predicted from finite element analysis.

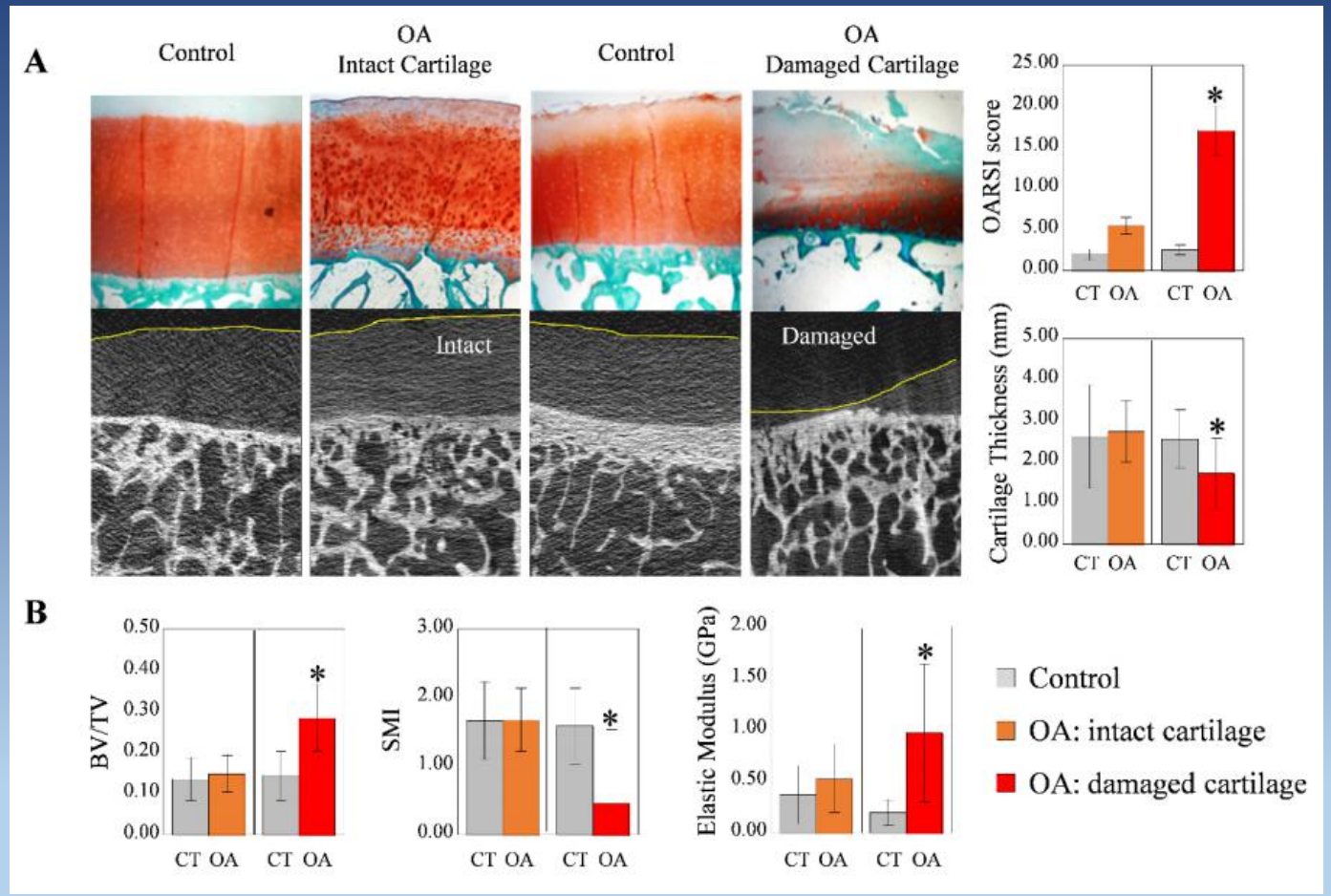


Figure 3. ITS detected subchondral bone changes beneath both damaged and intact cartilage in human OA.

We categorized the medial subregions as the damaged cartilage group, and the lateral subregions the intact cartilage group.

(A) Assessment of cartilage integrity by histological analyses and thickness measurement from µCT images.

(B) Conventional outcome measures of subchondral bone including bone volume fraction (BV/TV), structure model index (SMI, where 3 for pure rod-like and 0 for pure plate-like) and elastic modulus. **This indicated severe bone sclerosis.**

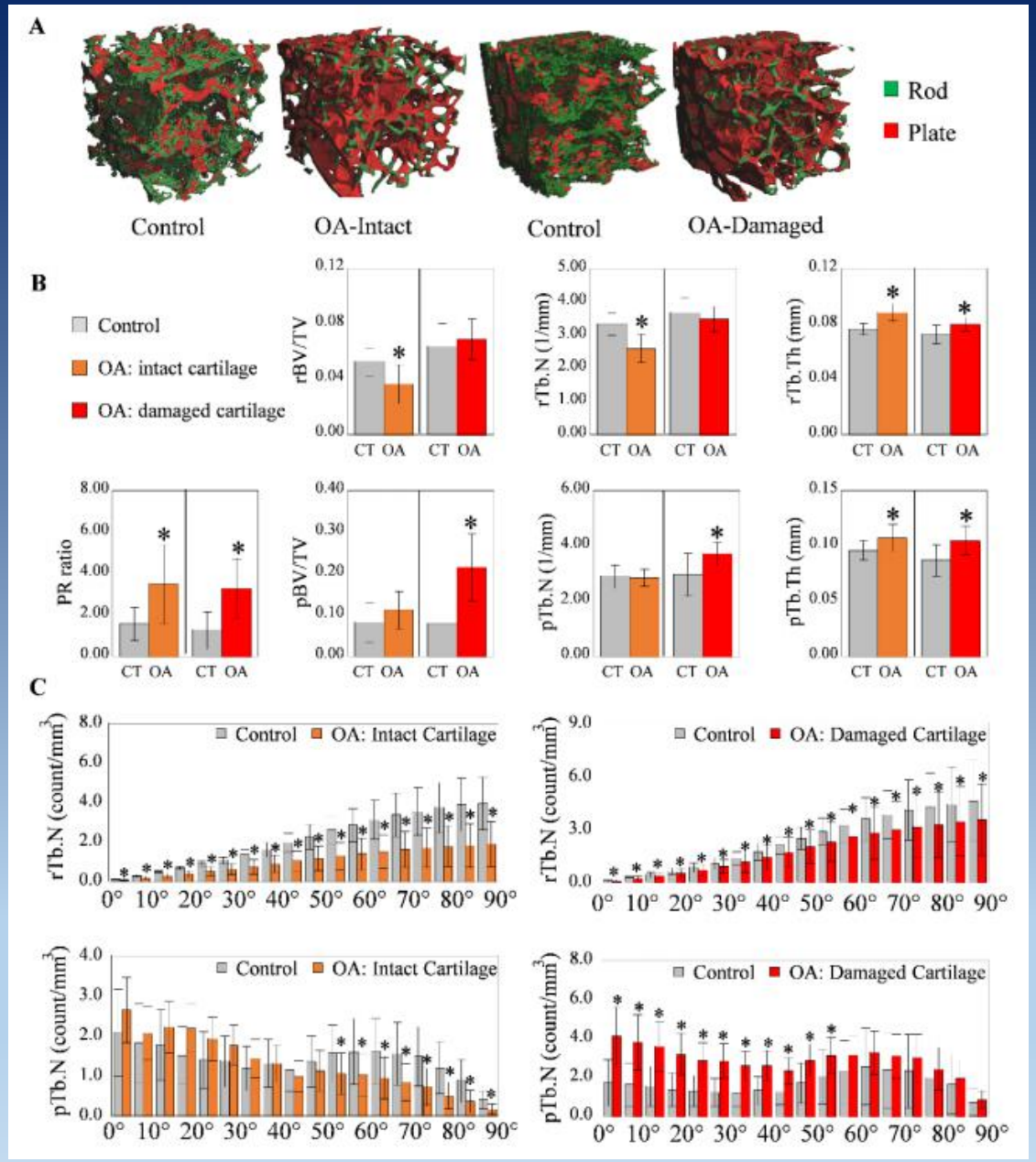


Figure 4. ITS detected subchondral bone changes beneath both damaged and intact cartilage in human OA.
We categorized the medial subregions as the damaged cartilage group, and the lateral subregions the intact cartilage group.
(A) Trabecular bone beneath intact and damaged cartilage segmented into trabecular plates (labeled in red) and rods (labeled in green) by ITS. **This demonstrated apparent reduction in trabecular rods in regions of both intact and damaged cartilage from OA samples.**
(B) Using morphological parameters from ITS to compare changes in the subchondral trabecular bone beneath intact and damaged cartilage. **This demonstrated that a significant increases in PR ratio in intact and damaged OA regions compared to control.**
(C) Orientation distribution of trabecular rods and plates from ITS analyses. **This demonstrated trabecular rod loss was uniform along all directions. Trabecular plates, on the other hand, decreased significantly along the oblique and transverse direction beneath intact cartilage, but increased significantly along the longitudinal direction beneath damaged cartilage.**

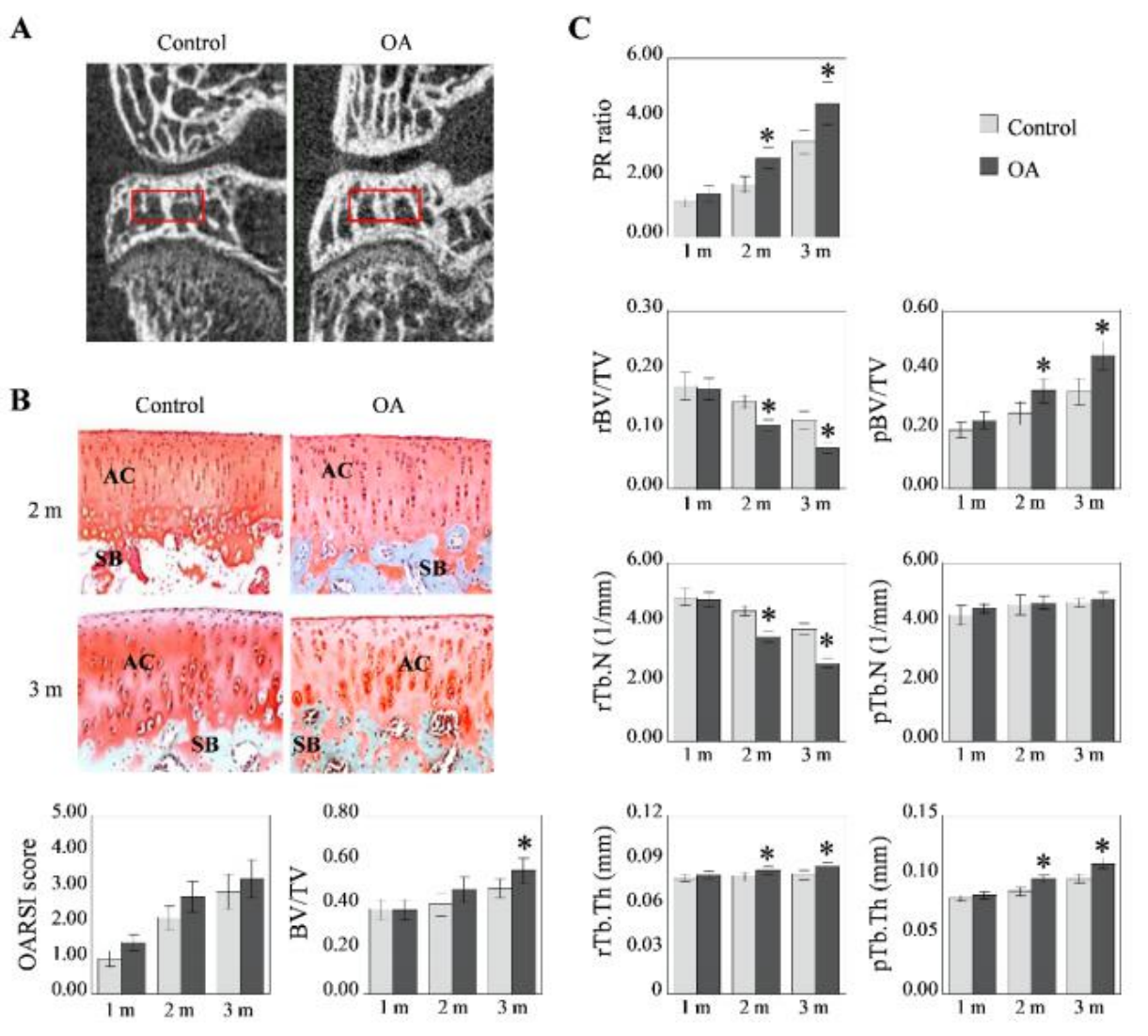
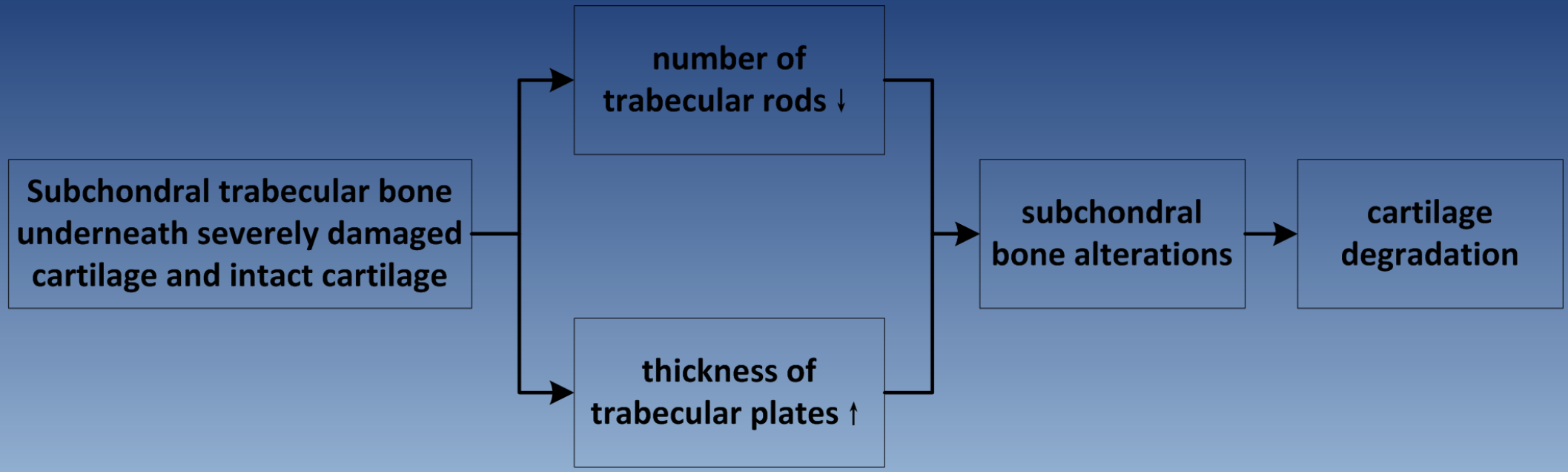
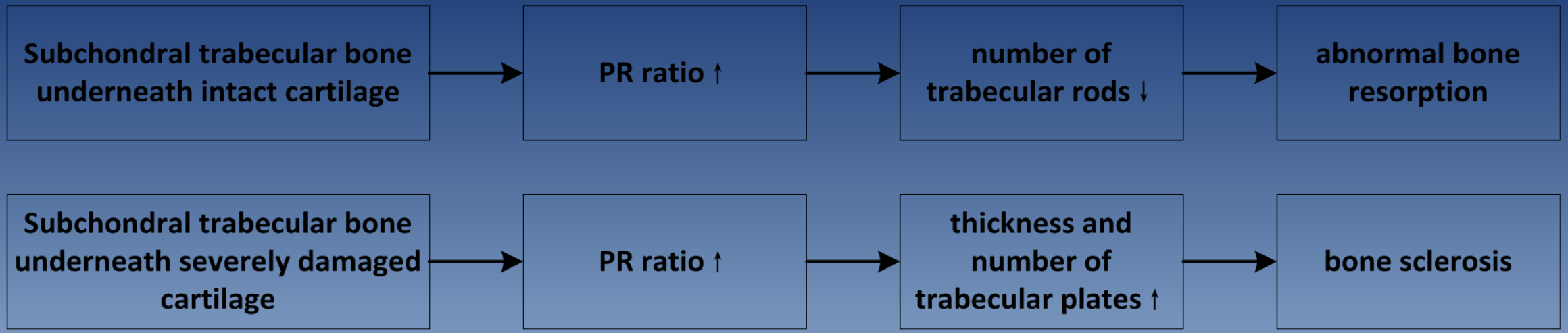


Figure 5. Subchondral trabecular bone changes precede cartilage degradation in guinea pigs with spontaneous OA.
(A) Reconstructed µCT image indicating region of interests (ROIs) on the medial tibial plateau from control and OA guinea pigs.
(B) Histological analyses and OARSI score as evaluations of cartilage integrity, and BV/TV as a general assessment of subchondral bone sclerosis. **This demonstrated that significant increases in BV/TV at month 3 in the OA strain.**
(C) ITS analyses of subchondral trabecular bone in the guinea pig at 1, 2, and 3 months of age compared to control. **These results indicated that these rod-and-plate microstructural changes in the subchondral bone preceded cartilage degradation in the guinea pig model of spontaneous OA.**

DISCUSSION



In this study, we investigated the microstructural and biomechanical changes in the subchondral bone in OA and their relationship to cartilage degeneration. By applying ITS, we discovered significant changes in the rod-and-plate configuration that were not apparent using conventional outcome measures. In human knees with advanced OA and guinea pig model of spontaneous OA, we found significant reductions in the number of trabecular rods and increases in the thickness of trabecular plates underneath severely damaged cartilage as well as cartilage that was still intact. These findings indicate that cartilage degradation may be secondary to subchondral bone alterations.



The underlying mechanism for increased PR ratio was different beneath intact and damaged cartilage regions. Beneath intact cartilage, the increased PR ratio was primarily due to reduction in the number of rods. Beneath damaged cartilage, however, this increase was primarily due to thickening and increase in the number of plates.

Trabecular rod loss that dominates in the intact regions may be indicative of abnormal bone resorption frequently reported in early OA. Trabecular plate thickening in the damaged regions, on the other hand, may be indicative of bone sclerosis, the hallmark of advanced OA.

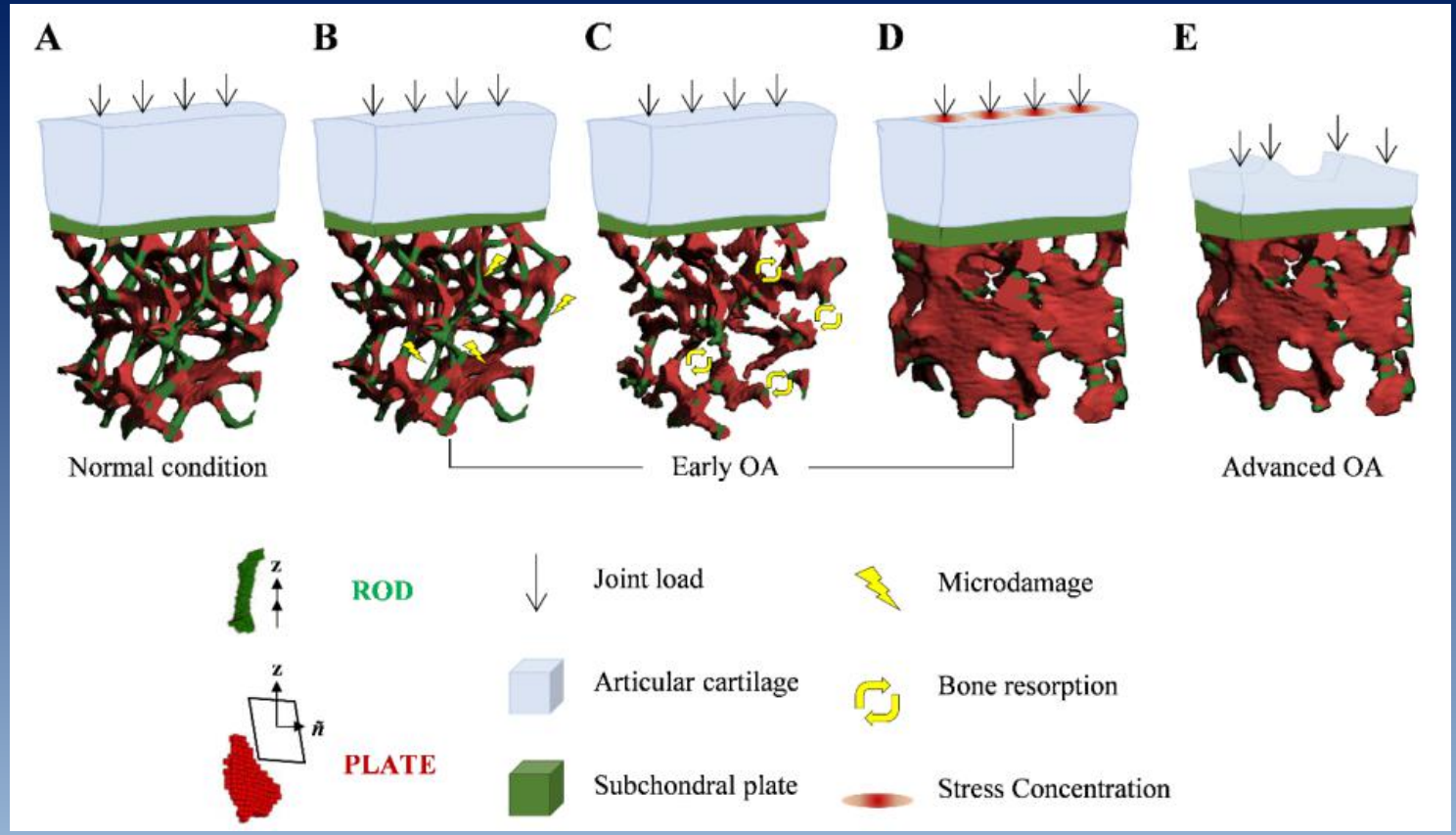


Figure 6. Schematic for a potential model for the pathogenesis of OA. In healthy knee, the subchondral bone is microstructurally optimized with a relatively even distribution of trabecular rods and plates, providing an even supporting bed for cartilage **(Fig. 6A)**. At the early stages of OA **(Figs. 6B, 6C, 6D)**, cartilage remains mostly intact, while abnormal bone resorption associated with trauma or microdamage due to abnormal mechanical stress (e.g., overloading in obesity) begin to attack trabecular rods. Trabecular rods are likely more vulnerable because they have higher surface-to-volume ratio and are relatively thinner than trabecular plates. Consequently, fewer load-supporting trabeculae result in higher mechanical demand distributed among the remaining trabeculae, which leads to trabecular thickening in the short term **(Fig. 6D).** Eventually, these microstructural changes disrupt the normal supporting bed for cartilage, resulting in an inhomogeneous distribution of rod-and-plate microstructure and local stiffening of the subchondral bone. These events can have devastating effects on the overlying cartilage. As a result, unfavorable mechanical conditions such as local stress concentrations could contribute to cartilage degradation in advanced OA **(Fig. 6E).**

In conclusion, we found that subchondral bone was characterized by trabecular rod loss and trabecular plate thickening in OA initiation and progression, and that these changes preceded cartilage degeneration. These results imply an important role of rod-and-plate microstructure changes of subchondral bone, especially trabecular rod loss, in OA pathogenesis. Furthermore, ITS-based analysis of rod-and-plate microstructure changes of subchondral bone can potentially be used in diagnosis of early OA and evaluation of OA progression.

THANK YOU