Zinc Enrichment and Mechanical Stiffening at the Tidemark as a Biomarker of Osteoarthritis Progression

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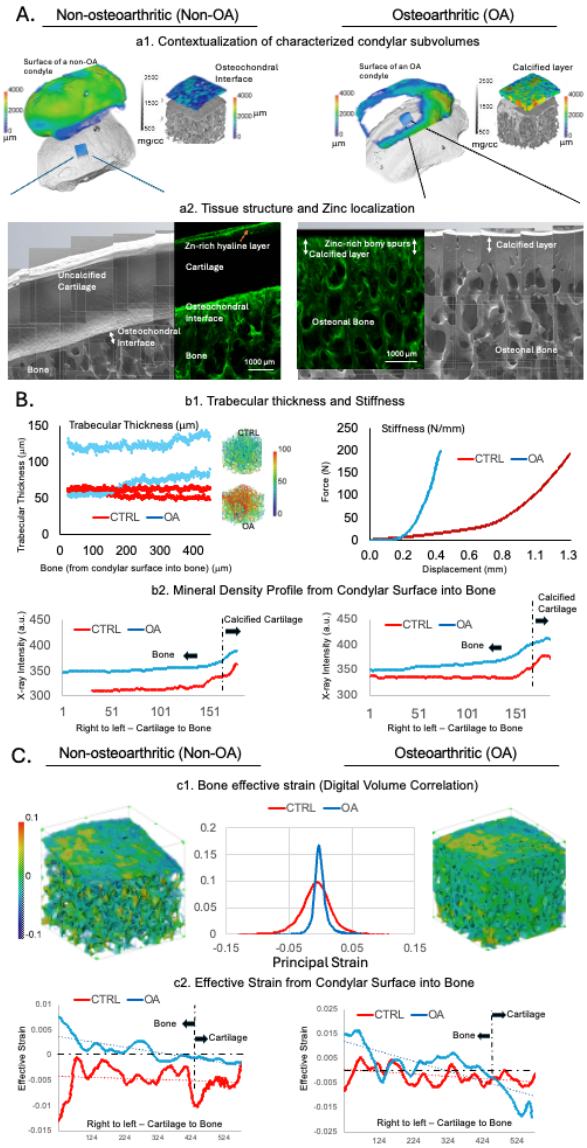

INTRODUCTION: Osteoarthritis (OA) is a progressive joint disease driven by biomechanical and biochemical alterations at the osteochondral interface (1, 2). The biomechanical competence of the osteochondral unit depends on the balance between collagen fibrillar networks providing tensile stiffness and proteoglycans supporting compressive resistance. Disruption of this balance alters strain distribution across the tidemark and predisposes cartilage and bone to damage (3). In addition to structural remodeling, trace element homeostasis plays a critical role in joint health (4). Zinc (Zn) is essential for cartilage and bone metabolism, influencing metalloproteinase activity, collagen cross-linking, and chondrocyte function. Altered Zn concentrations have been detected in osteoarthritic cartilage, meniscus, and ligament tissue, with enrichment at sites of degeneration (5). Elevated or redistributed Zn may contribute to pathological mineralization, while deficiencies impair cartilage matrix organization and bone formation (3). Increased Zn levels in hydroxyapatite demonstrated mechanical reinforcement and acted as a load-transfer element to transmit stress into underlying tissue layers (6, 7). Despite these observations, little is known about how Zn distribution correlates with mineral density, stiffness, and energy dissipation at the tidemark in human knee joints. Establishing this relationship could identify physicochemical biomarkers of OA progression, providing mechanistic insights into osteochondral stiffening and risk to failure. We therefore hypothesized that Zn enrichment co-localizes with mineralization and stiffness at the tidemark, reducing energy dissipation and predisposing joints to OA progression.

METHODS: Tibial condyles from knee joints of patients undergoing total knee arthroplasty (male, 70 years, BMI 39.43; female, 67 years, BMI 33.6) were examined. One side of the condyle displayed severe OA, while the contralateral side with no clinical evidence of OA served as an internal control. Zinc distribution was mapped using synchrotron-based X-ray fluorescence (XRF) microprobe at beam line 10.3.2 at the Advanced Light Source, Lawrence Berkeley National Laboratory. Mineral density and microarchitecture were quantified by micro-XCT (MicroXCT-200, Carl Zeiss X-ray Microscopy, Pleasanton, CA). Mechanical loading experiments (MT10352, 500 Nano Tomography, Deben UK Limited, West Sussex, UK) were conducted under progressively increasing compressive force at a motor speed of 0.5mm/min and a peak load of 200N to evaluate stiffness, energy dissipation, and strain fields (8).

RESULTS: Both OA specimens exhibited increased trabecular thickness (A-a1, a2; B-b1), increased mineral density within calcified cartilage relative to uncalcified cartilage (A-a1, B-b2), and increased stiffness and decreased energy dissipation (B-b1) compared to contralateral side. The OA specimen displayed a markedly thick calcified cartilage zone, near absence of uncalcified cartilage, and zinc-enriched osteophytes/bony spurs (A-a2). In contrast, the non-OA side exhibited a zinc-rich layer on the articulating surface of the condyle and distinct zinc accumulation at the osteochondral interface (A-a2). Mixed strain profiles within the volumes of both OA and non-OA condyles were observed (C-c1). In the OA condyle, strain decreased in cartilage but sharply increased within subchondral bone, in contrast to uniform strain distribution across the osteochondral unit in the non-OA (C-c2). In summary, the OA side demonstrated increased trabecular thickness, higher bone mineral density, higher effective stiffness, and reduced energy dissipation, alluding to increased failure risk.

DISCUSSION: Our findings indicate that OA progression involves coupled physicochemical and mechanical alterations at the tidemark. The loss of uncalcified cartilage, excessive mineralization, and zinc redistribution coincide with strain focusing on the bone and progressive adaptation with increased trabecular thickness, showing reduced capacity for energy dissipation. This stiffening renders the joint more susceptible to failure.

SIGNIFICANCE: This case study illustrates the potential of zinc mapping, when combined with mechanical testing, to serve as an early physicochemical biomarker of OA progression. Such biomarkers could complement current imaging diagnostics, providing mechanistic insights into osteochondral stiffening and informing strategies for early diagnosis and intervention. These strategies need not be limited to the knee joints and can be extrapolated to the seemingly dissimilar yet diarthrodial joint such as the temporomandibular joint (TMJ) to investigate TMJ associated osteoarthritis.

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