WORKSHOP

Bone Marrow Lesions - What Lies Beneath?
A workshop based on the ORS/AAOS symposium: Tackling Joint Disease by Understanding Crosstalk between Cartilage and Bone, April 2016

Organizers:
Oran D. Kennedy, PhD
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Speakers:
David Felson, MD
David Findlay, PhD
Christopher Hernandez, PhD

<u>ORS Workshop: 'Bone Marrow Lesions - What Lies Beneath?', San Diego 2017</u>

Organizers:

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Speaker 1: *Prof. David T. Felson MD MPH, Professor and Director, Clinical Epidemiology Research & Training Uni. Boston University School of Medicine, 715 Albany Street, USA*

Title: Bone Marrow Lesions in Osteoarthritis: Epidemiology and Clinical Imaging

Abstract

In osteoarthritic joints, bone marrow lesions (BMLs) are poorly circumscribed white spots seen on fat suppressed MRIs located underneath the cortical bone envelope. Histology and histomorphometry of these lesions have demonstrated the presence of fibrosis, necrosis and reversal lines of bone, suggesting that these lesions represent areas that have undergone bone trauma / microcracking and subsequent damage responses. Transarticular malalignment in the knee joint has also been shown to cause BMLs in regions where the stress field has been increased (e.g. varus knees → medial BMLs; valgus knees → lateral BMLs). Furthermore, tears and damage to the meniscal structures of the knee also lead to BMLs in the region of the tear. BMLs have also known to be dynamic phenomena; enlarging BMLs are associated with the development of pain in knee osteoarthritis and shrinking BMLs with pain reduction, providing evidence that these lesions are a cause of knee pain in osteoarthritis. Longitudinal studies have shown that BMLs predict structural progression of osteoarthritis with cartilage loss occurring in regions overlying the BML. In recent clinical trials of persons with painful knee osteoarthritis, zoledronic acid, a bisphosphonate, has been found to shrink BMLs and reduce pain. Using novel intervention for address this issue our group showed that patellar bracing could reduce the size of patellofemoral BML, although not the tibiofemoral, and diminish knee pain.

Speaker 2: *Prof. David Findlay, PhD, Professor of Orthopaedic Research in the Discipline of Orthopaedics and Trauma, University of Adelaide. University of Adelaide, Australia.*

Title: Bone-Cartilage Crosstalk in Joint Injury and Disease: A Biological Perspective

Abstract

In human osteoarthritis (OA), and in animal models of OA, degraded cartilage overlies subchondral bone that also shows characteristic changes, including bone sclerosis, vascular pathology, and bone matrix microdamage. The occurrence of disease-associated changes in these two tissue compartments, seemingly simultaneously, has given rise to the notion of 'bone-cartilage crosstalk', whereby signals from cartilage to bone and vice versa exacerbate the disease process. If this crosstalk exists, it could be biomechanical, biochemical, or both. Alternatively, it could be that cartilage and bone each respond independently to the same acute or chronic insults to the joint, in particular injury and overloading. These mechanical insults may be overlayed with metabolic drivers, since many individuals suffering with OA have co-morbidities, including hypertension, diabetes and vascular disease. This talk will examine the evidence that biochemical and biomechanical signalling between these tissue compartments is important in OA disease progression. Several key questions will be addressed. Firstly, do these tissue compartments communicate? If so, is this communication important in health and disease? What is the nature of the communication? What are the changes that take place in bone and cartilage during OA development and how might these changes in either tissue affect the other? Since the evidence to date comes largely from animal and in vitro studies, how might information of human OA be obtained, other than at end-stage disease? If there is crosstalk between bone and cartilage that is important in the development of OA, could this provide therapeutic targets? Should therapies be targeted to bone or cartilage?

Speaker 3: *Prof. Christopher J. Hernandez, Ph.D. Associate Professor Sibley School of Mechanical & Aerospace Engineering and Meinig School of Biomedical Engineering, Cornell University, Ithaca, NY*

Title: The Role of Microdamage and Bone Remodeling in Joint Injury and Disease

Abstract

Bone marrow lesions (BMLs) are one of the "hallmarks" of osteoarthritis and are associated with pain increased likelihood of joint replacement and subchondral bone attrition. BMLs can fluctuate in size over time and can resolve spontaneously or enlarge and contribute to joint degradation and pain. Developing our understanding of these lesions may provide a long-sought marker for diagnosis of osteoarthritis before substantial cartilage degeneration. Unfortunately, we know relatively little about the mechanisms involved in the initiation or progression of BMLs. Two facts are clear, however. First, they are associated with regions of cancellous bone experiencing increased mechanical stress. Even minor increases in mechanical loading such as increased standing, or subtle changes in gait may initiate BML formation; suggesting that habitual loading as well as traumatic loading can generate a BML. Second, biopsies of BMLs collected at the time of joint arthroplasty display a combination of increased bone remodeling, microscopic tissue damage/abnormal trabeculae, woven bone and increased vascularity. These facts suggest a role of physical forces, bone remodelling, and repair of tissue microdamage as contributors to the initiation or persistence of BMLs. However there are substantial gaps in our understanding of BMLs. Histopathology is available for late-stage BMLs, but very little is known about early stage BMLs that may still be reversible. Specifically how tissue microdamage contributes to BMLs is not yet known.

In this session we review the potential mechanisms underlying BMLs including how mechanical loads are distributed within subchondral cancellous and cortical bone, how tissue microdamage forms in cancellous bone, the relationship between tissue microdamage and remodeling and how changes in bone remodeling can influence cancellous bone mechanical performance. Cancellous bone carries a substantial component of the loads applied across the joint and tissue microdamage can form without failure of the surrounding cortical shell. Tissue microdamage can be generated in subchondral cancellous bone following low energy trauma and is present in otherwise normal human tissue. Once present in cancellous bone tissue, microdamage can have a substantial effect on bone stiffness and strength, but the effect is threshold driven and requires accumulation of sufficient microdamage (more than 1% DV/BV) before noticeable impairment of cancellous bone mechanical properties. Tissue microdamage is known to stimulate bone resorption and remodeling in cortical bone, but the effect in cancellous bone has not been studied and there is evidence that tissue microdamage in cancellous bone may instead stimulate rapid bone formation in the form of a microcallus or aberrant bone formation. Additionally, the generation of microdamage in cancellous bone is sensitive to tissue material properties. Lastly, increases in tissue stress and strain in cancellous bone are known to simulate new bone formation suggesting that cancellous bone within a BML may be adapting to mechanical loads as well as responding to tissue microdamage.

Summary

There remain substantial gaps in our understanding of how BMLs form, persist and progress in instances of joint injury and disease. Recent research has shed much light on these issues and we made progress in addressing some of these gaps. Furthering our understanding the mechanisms underlying initiation and persistence of BMLs has the potential to lead to exciting new therapies and interventions that could help predict and mitigate progression of joint disease.

Key References

Burr DB, Gallant MA. (2012) Nat Rev Rheumatol. 8:665-673.

Zhen G, et al.(2013) Nat Med. 19:704-712.

Findlay, DM, Atkins, GJ. (2014) Curr Osteo Reps. 12:127-34.

Yuan XL et al. (2014) Osteo Cart. 22:1077-1089.

Findlay DM, Kuliwaba JS. (2016) Bone Res 4:16028.

Muratovic D et al (2016) Arthritis Res Ther. 18:54, 2016.

Ko FC, et al. (2016) J Orthop Res. 34:1941-1949.

Dore D, et al. (2010). Arthritis Res Ther 12(6): R223.

Hunter DJ, et al. (2011). Osteo Cart 19(5): 557-88.

Roemer FW, et al. (2010). Osteo Cart 18(1): 47-53.

Felson DT, et al. (2012). Osteo Cart 20(12): 1514-8.

Felson DT, et al. (2014). Rheum Dis Clin North Am 40(4): 699-710.

Eriksen EF, et al. (2012). Rheumatol Int 32(3): 575-84.

Zanetti M, et al. (2000). Radiol 215(3): 835-40.

Taljanovic MS, et al. (2008). Skeletal Radiol 37(5): 423-31.

Muratovic D, et al. (2015). Arthritis Res Ther 18: 54.

Hernandez CJ, et al. (2014). Bone 66: 205-13.

Zhen G, et al. (2013). Nat Med 19(6): 704-12.