Citation: IBMS BoneKEy **10**, Article number: 448 (2013) | doi:10.1038/bonekey.2013.182

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MEETING REPORT

Bone fatigue, stress fractures and bone repair (Sun Valley 2013)

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IBMS BoneKEy **10,** Article number: 448 (2013) | doi:10.1038/bonekey.2013.182; published online 13 November 2013

Meeting Report from the 43rd International Sun Valley Workshop, Musculoskeletal Biology, Sun Valley, ID, USA, 4–7 August 2013

Interactions between mechanical fatigue in bone, stress fractures and bone repair processes were the topic of this session at the IBMS Sun Valley workshop in August 2013. The workshop included invited talks by Jeffery Nyman, PhD, Christopher J Hernandez, PhD, Mitchell B Schaffler, PhD and Elizabeth Shane, MD. In addition, the session included talks by two recipients of the ASBMR Harold M Frost Young Investigator awards: Sarah H McBride, PhD and Eve Donnelly, PhD. The session concentrated on the pathophysiology of stress fractures and atypical femoral fractures associated with the long-term anti-resorptive therapy.[1]

Stress fractures are a type of fracture that results from repeated loading at magnitudes well below the level required to break the bone during a single load. The first clinical reports of stress fractures are attributed to Briethaupt, who noted foot pain in soldiers following long marches.[2,3] Pentecost *et al.*[4] classified two different forms of stress fracture: a fatigue fracture and an insufficiency fracture (**Figure 1**). A fatigue fracture is defined as a stress fracture resulting from excessive cyclic loading on otherwise normal bone, whereas an insufficiency fracture is defined as a stress fracture from normal loading that occurs in bone with compromised mechanical properties. Research on stress fractures has concentrated on fatigue fractures, which are most often observed in high-performance athletes and military personnel. In the current session, emphasis was placed on insufficiency fractures, which are more common in individual with osteoporosis. It is now believed that atypical femoral fractures are a type of insufficiency fracture.[5]

Insufficiency fractures develop over weeks or months.[5,6] Because insufficiency fractures develop over time, they may be influenced not only by mechanical damage but also by the remodeling/modeling activity that occurs after the formation of tissue damage (**Figure 2**). The session included four invited speakers; each addressed one component of the proposed pathophysiology of stress fractures and sought to address the key unanswered questions in the field (**Figure 3**). Although bone strength is commonly expressed as mechanical failure from a single loading event, fatigue failure of bone occurs as a result of multiple loading events. Fatigue failure is measured as the number of cycles to failure at a specified applied stress. Bone strength and fatigue properties are related to one another but are distinct mechanical properties of the bone tissue. Fatigue failure is more sensitive to the degree to which the tissue can resist the formation and propagation of microscopic cracks. The ability of bone tissue to resist the formation and propagation of microscopic cracks is influenced by bone tissue ultrastructure and chemical properties including bound water, collagen crosslinking, osteopontin and matrix metalloproteinases.

Although fatigue fractures are more commonly observed in cortical bone, insufficiency fractures are more commonly observed in regions of the skeleton dominated by cancellous

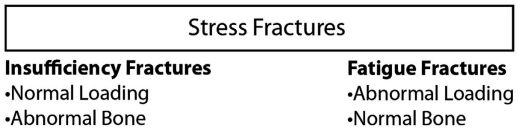

Figure 1 The two types of stress fractures as classified by Pentecost *et al.*[4] are contrasted.

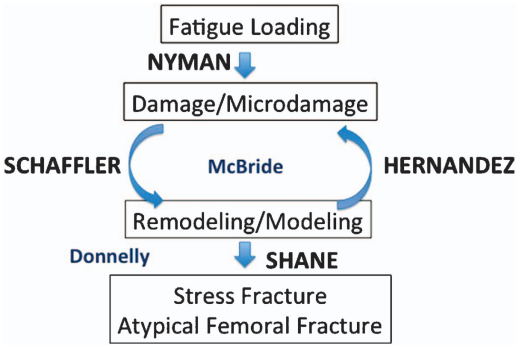

Figure 2 The proposed pathophysiology of stress fractures is illustrated. Stress fractures are the result of tissue damage and microdamage caused by repeated fatigue loading as well as interactions between tissue damage and bone remodeling and repair processes. The name of each speaker in the session is listed next to the component of the stress fracture etiology that was addressed in his/her talk.

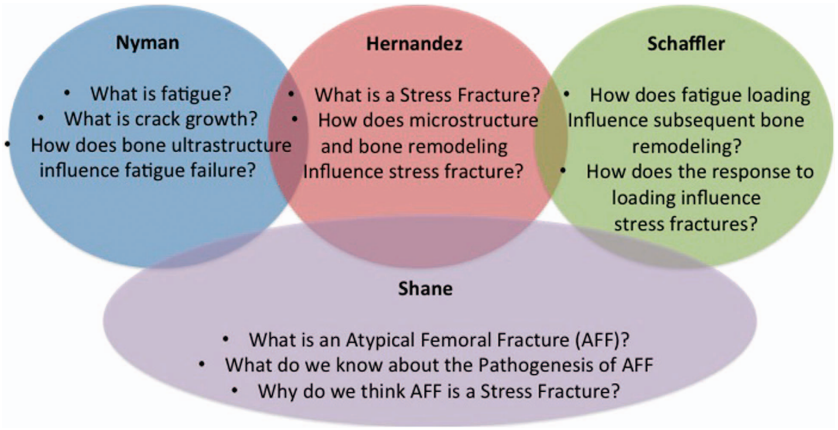

Figure 3 A Venn diagram illustrating the questions raised by each of the invited speakers as well as content overlap.

bone. During the development of an insufficiency fracture, there is an accumulation of microscopic tissue damage and an associated degradation in bone biomechanical performance. Small amounts of microscopic tissue damage are associated with large reductions in cancellous bone Young's modulus, strength and fatigue life. Findings over the past decade have demonstrated that the formation of microscopic tissue damage initiates a local cellular response that may also contribute to the development of an insufficiency fracture. In cortical bone, the generation of microdamage results in apoptosis in neighboring osteocytes.[7] Those osteocytes that do not undergo apoptosis express RANKL, thereby triggering an additional bone resorption,[8] which allows the removal of microdamage but may also create stress risers that may promote the formation of more microdamage.[9]

Atypical femoral fractures associated with long-term treatment with anti-resorptive agents have been classified as insufficiency fractures.[1] Although the risk of atypical femoral fractures is much lower than the risk of conventional osteoporosis-related fractures (the risk of a hip fracture is more than seven times greater than the risk of atypical femoral fractures), given the widespread use of anti-resorptive therapies, there is a great need to understand the pathophysiology of atypical femoral fractures and identify the individuals at risk. Alterations in bone tissue ultrastructure have been implicated as contributors to the pathogenesis of atypical femoral fractures.

The session discussions highlighted the need to better understand the interactions between bone quality, bone tissue damage accumulation and repair processes. Bone marrow edemas detected through magnetic resonance imaging are believed to be incomplete insufficiency fractures, but little is known about which bone marrow edemas will eventually lead to an insufficiency fracture and which will resolve on their own. It remains possible that some low-energy fractures are the result of an overload applied to a bone already weakened by an incomplete insufficiency fracture. Bone marrow edemas associated with insufficiency fractures are similar to bone marrow lesions associated with the development of osteoarthritis, but the connection between the two is not yet clear. Insufficiency fractures are the result of microdamage accumulation and repair but not all forms of microdamage in bone tissue are the same; some forms of microdamage require bone remodeling repair processes, whereas other types of microdamage disappear without remodeling. Although atypical femoral fractures appear to occur through mechanisms similar to those seen in insufficiency fractures, there remain many questions about the pathogenesis of atypical femoral fractures and potential approaches to prevent atypical femoral fractures.

Conflict of Interest

The author declares no conflict of interest.

Acknowledgements

This study was supported by NIH/NIAMS R01AR057362. The author has received research support from the Musculoskeletal Transplant Foundation and AMGEN.

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