IN VIVO AND IN VITRO IMAGING FOR BONE REGENERATION

Ming Ding, MD, PhD, DMSci
Department of Orthopaedic surgery and Traumatology, Odense University Hospital, University of Southern Denmark, Denmark

Today 2.2 million bone-graft surgeries have been performed annually on world basis, resulting in a demand for bone graft that far exceeds supply. As a consequence, a variety of biomaterial scaffolds have been developed for tissue engineering of bone healing and repair. The structure of scaffolds is of particular importance in scaffolds-based tissue engineering since it affects the functionality of the tissue-engineering construct. Preclinical investigations of bone regeneration with scaffolds have been performed using various animal models, and bone regeneration has been evaluated by different methodologies. Micro-CT imaging provides an important analytical tool capable of quantifying bone tissue in vitro, and more importantly of monitoring bone formation in vivo longitudinally. This technique provides a fast, nondestructive, and 3D quantification of bone scaffolds, and bone formation and ingrowth.

Currently, methods for quantitatively assessing macrostructure include conventional radiographs, dual-energy X-ray absorptiometry (DEXA) and computed tomography (CT), particularly volumetric quantitative computed tomography (vQCT). Methods for non-invasive assessing microarchitecture of bone tissues include high-resolution peripheral quantitative computed tomography (HR-pQCT), microcomputed tomography (micro-CT), high-resolution magnetic resonance (HR-MR), micromagnetic resonance (micro-MR), synchrotron radiation computed tomography (SR-CT). Methods for non-invasive assessing ultrastructure of bone tissues can be achieved by nano-CT scanner and SR-CT. vQCT, HR-pQCT and HR-MR are generally applicable in vivo as clinical tools for assessment of bone diseases and bone repair; micro-CT and micro-MR are applicable both in vivo in patients and in animals, and in vitro for animal sample and human bone biopsy as well; and SR-CT is applicable in vitro. During the last decades, great progresses in imaging techniques have been achieved allowing us to monitor bone microarchitectural changes in vivo in a non-invasive manner and ultrastructural changes in vitro with high accuracy. Imaging can reach a high resolution as micrometer or even nanometer scale. However, more efforts are demanded to improve imaging techniques. This review concentrates on quantification of in vivo micro-CT imaging for small animal longitudinal studies; in vitro micro-CT and nano-CT imaging for sample assessments; and HR-pQCT for clinical trials. These imaging techniques allow us to analyze hierarchical structures of cancellous bone, cortical bone, and bone regeneration, and to characterize them into organ level, tissue level, and cell level.

Brief CV
Research Area(s): Bone imaging, biomaterials, bone regeneration, clinical trials
Technical Expertise: Bone microarchitecture, ultrastructure, biomechanics, animal models, RSA analysis, histomorphometry
Email: ming.ding@rsyd.dk
Website: www.sdu.dk/ki/orthe

M. Ding is a professor at the Department of Orthopaedics and Traumatology, Odense University Hospital, Institute of Clinical Research, and University of Southern Denmark. He is the leader and supervisor for the experimental projects going on at the Orthopaedic Research Laboratory and the Roentgen Stereometric Analysis (RSA) Laboratory, and is responsible for national and international collaborations. He received MD, bachelor of medicine in 1984, master of medicine in 1990 (China), PhD in Medicine in 1999 (Aarhus), and Doctor of Medical Science (DMSc) in 2010 (Aarhus). He has 20 years’ orthopaedic research experience in Odense/Aarhus, Denmark, particularly focusing on the field of bone micro-CT/nano-CT imaging and microarchitecture/ultrastructure, biomechanics, histomorphometry, biomaterials, tissue engineering, bone regeneration, RSA technique and clinical trials, and experimental orthopaedic surgery in large and small animal models. He has supervised 28 candidate students, PhD students and Postdocs. He is a reviewer for 26 international peer-review journals and 4 international research grants. He is editorial board member of 2 peer-review journals. He received a number of awards including the Goring Selvix Prize. He has been teaching medical/biomedical/sport medicine students and PhD students, and given 21 invited lectures at international conferences and university institutes. M. Ding as principal investigator or co-Investigator has received many research grants including 3 EC research grants. He is an author of 72 publications, and 91 international conference abstracts (Publication citation summary: in total 2100 citations; h-index = 23, source Science Citation Index — SCI).

BIOMAGING AND SMALL ANIMAL MODELS IN DRUG DEVELOPMENT FOR MUSCULOSKELETAL DISORDERS

Jürg Andreas Gasser
Novartis Institutes for Biomedical Research, Switzerland

Muscle atrophy is common in aging (sarcopenia), as a consequence of fractures or bed rest (disuse atrophy) and as a result of chronic illnesses like cancer, COPD and chronic infections (cachexia). Loss of mobility due to muscle weakness and atrophy is a common and debilitating problem across all ages leading to increased morbidity and mortality. Although there is proven efficacy of resistance exercise, this is very hard to scale up to population-level treatment. There is no pharmacological treatment that can reverse muscle atrophy. Pharmacological treatment can be aimed at blocking the diseases related atrophy, stimulating a muscle hypertrophy, encouraging satellite cells to undergo cell differentiation, stimulating fiber-type switch or mitochondrialogenesis, and at improving neuromuscular coupling.

Disease progression and drug treatment effects on muscle can be evaluated in a large array of rodent models. These include sarcopenia as a result of spontaneous aging, dexamethasone-induced myopathy, mouse boot immobilization, denervation or nerve crush-damage induced atrophy, as well as cancer or adjuvant arthritis induced cachexia. Muscle volume can be determined non-invasively with high precision in rodent models using proton MRI and qMRS. Quantification of muscle fiber type composition requires tissue sampling and automated quantification by histomorphometry. Methods to quantify energy metabolism using 31P magnetic resonance spectroscopy (31P MRS) for widespread use in small animals are in development. There appears to be a good agreement between changes in O2 saturation and phosphocreatine concentrations.

The ultimate therapeutic goal in treating muscle wasting disorders is the improvement in muscle function which, unfortunately, oftentimes correlates poorly with changes in muscle volume as determined by non-invasive imaging. For this reason, physical performance testing (treadmill performance testing), determination of muscle strength (evoked muscle force and fatigue), endurance exercise and gait analysis remain essential tools for monitoring of disease progression and the determination of therapeutic effects, which at present cannot be replaced by non-invasive bioimaging methods. In the future, a minimally invasive ‘optical’ biopsy with the sarcoscope, may be able to assess muscle contractile dynamics in mice and humans.

Brief CV
Research Area(s): Between 1990 and 2000: Preclinical characterization of novel and proprietary pharmaceutical products for the treatment of metabolic bone disease including cathepsin K inhibitors, c-src inhibitors, SERM’s, bisphosphonates, analogs of PTH and calcilytics. Use of mesenchymal stem cells for bone and cartilage regeneration in collaboration with Osiris Therapeutics. Between 1990 and 2008: Identification of novel bone anabolic targets, based on investigation of the biochemical pathways leading to high bone mass phenotypes in human and murine genetic mutations such as LRPS, and gene

Abstracts