Translational Research:
Biomechanical and Biological Events Associated with Osteoarthritis
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The Osteoarthritic Workshop developed the following consensus definition (*Kuettner, K.E., V.M. Goldberg, 1995);* "**Osteoarthritic diseases (OA)** are a result of both mechanical and biological events that destabilize the normal coupling of degradation and synthesis of articular cartilage chondrocytes and extracellular matrix, and subchondral bone. … Although they may be initiated by multiple factors, including genetic, developmental, metabolic, and traumatic, OA diseases involve all of the tissues of the diarthrodial joint." While the symptoms of OA are well known (pain, joint space narrowing, cartilage fibrillation and eburnation, subchondral bone cysts), scientists are still uncovering the root causes of the disease.

Arthritis affects more than 15% of USA (over 43 million) with a direct medical cost $15 billion nationally. Total costs (ie direct and wages) were estimated in 1992 as $65 billion. OA affects 20.7 million people in the US greater than 45 years of age. Due to the demographic trends by 2020 (aging baby boomers), 18% of the US (≈60 million) are anticipated to have some form of arthritis with a commensurate increase in cost. A leading cause of disability in the United States, OA is one of the most urgent research challenges of twenty-first century medicine. Based upon prevalence, a focus upon the knee is recommended as a model for Osteoarthritis (Cushnaghan and Dieppe (1991), Jordan et al (1995)). Xray features (joint space narrowing and osteophytes) may lag the original structural changes of OA by years such that current epidemiology may underestimate disease prevalence (Rodgers et al (1990)). Novel and reliable methods for early detection of OA **(disease onset)** are very important towards the goal of developing effective treatments that can modify the course of the disease.

Osteoarthritis has been associated with three primary biomechanical factors: (1) increased BMI, (2) injury, and (3) malalignment. Continued epidemiology efforts that are coupled with biomechanical and biological data are needed to establish and/or confirm risk factors for disease onset and progression for the osteoarthritis diseases. **Epidemiology that is coupled with biomechanical measures** should help advance our understanding of OA risk factors in part due to the larger sample sizes incorporated in public health studies which is rare in biomechanical investigations.

Baby boomers are anticipated to need a significantly increased number of total joint replacements with much of their OA in process from one or more of the previously mentioned risk factors. Fortunately, total knee replacements (TKR) are successful for the vast majority of individuals with reasonable survivorship. Still, TKR recipients do not have normal gait, even at several years post-op. Younger people with obesity and/or malalignment and athletes with injuries (eg. ACL or meniscal tears) may have the most to gain from an OA initiative. The focus needs to be on **early detection**: assessment of risk factors, from the perspective of disease onset, progression, effective treatment, and prevention.

The **link between aberrant biomechanics and pathophysiology** needs to be further investigated in both animal models and in vivo. There is a need for improved animal models to assess the factors associated with **OA progression** (eg inflammation). Although a fair amount has been learned, models are needed where the investigators can control the variables. Ultimately what is learned from animal models in terms of subchondral bone biology, enzyme degradation of cartilage matrix, inflammatory mediators, and markers of cartilage matrix breakdown must be translated to human subjects and related to disease severity.

Clinical registries of primary (non-traumatic onset) and secondary OA (eg. ACL or meniscus injury), the pertinent biomechanical and biological factors, and treatment outcomes are required to understand the impact of treatment upon disease. Improved measures of joint integrity (eg. multidirectional flexibility in the presence of joint instability and objectives measures of pivot shift that go beyond the KT1000) are required. Non-invasive, but objective, measures of diarthrodial joint integrity are needed. Refinement of tools such as the

magnetic resonance image (MRI) into objective measures for soft tissue assessment from both the macro-structural (eg. meniscal displacement, tears, etc) and micro-structural (eg. collagen fiber orientation, proteoglycan concentration, etc) perspectives are needed to better understand clinical presentation of OA.

Computational models of OA are needed that can accurately predict kinematics, kinetics, and joint stresses to serve as a tool to explore the interaction between alignment, BMI, and injury in disease pathomechanics. Given that joint stress cannot be directly measured in vivo such tools will be required to effectively modify the aberrant mechanics operating about a given patient's joint. Validated computational models should be encouraged to include subject specific geometries of osseous and soft tissue structures, appropriate material properties, and the effect of muscle-tendon and well as gravitational loading as required by the hypothesis under study.

OA is a disease of all the tissues within the diarthrodial joint: cartilage, synovium, and bone. Research that examines the **relationship between structure and function** at the cellular, tissue, and whole body scales is recommended. **Clinical outcomes** of both conservative (eg. viscosupplements, pharmaceutical, nutraceutical, orthoses such as knee bracing, physical therapies, etc) and surgical (eg. reconstructive surgery, realignment surgery, cartilage transplantation, resurfacing, joint fusion, partial and total joint replacement, etc) procedures are essential to determine which approaches are palliative for pain relief and which, if any, are disease modifying. In addition to the standard patient self-assessments of pain and function, studies incorporating 3D motion analysis during functional tasks (eg gait, posture, sit-to-stand, stair ascent/descent) are needed to determine the functional limitations/disabilities associated with each stage and etiology of the osteoarthritic diseases. In this way, the impact of a given treatment upon pain and function maybe objectively assessed. Such clinical outcome studies should be encouraged to incorporate basic science components of OA (eg bone biology, synovial fluid and serum analysis, MR based collagen alignment, skeletal alignment, etc) to establish the bi-directional flow of information that is the basis for truly translational research.

1. Kuettner, K.E., V.M. Goldberg, 1995
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4. Healthy People 2010
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6. Rogers, J., I. Watt, and P. Dieppe, Comparison of visual and radiographic detection of bony changes at the knee joint. Bmj, 1990. 300(6721): p. 367-8.