Introduction: A Single-Topic Issue on Mechanobiology

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The articles in this single topic issue of the Journal of Rehabilitation Research & Development concern the regulation of skeletal tissue biology by mechanical stimuli, a topic which we refer to as “mechanobiology.” The specific scientific approach of the studies presented ranges widely, from fundamental studies using in vitro systems, computer and animal models to more applied studies already influencing or defining clinical practice.

The mechanobiology of connective tissues lies at the heart of two of the most common skeletal diseases in the elderly—osteoarthritis and osteoporosis. Because of the aging of our population, the prevalence of these diseases is increasing each year. At the start of the 20th century, individuals over the age of 65 represented less than 4 percent of the US population. As we enter the 21st century nearly 13 percent of our population is 65 or older and by the year 2030 this figure is expected to climb to 22 percent: nearly 1 out of every 4 individuals. People are living longer and orthopaedic diseases are having a serious impact on the quality of life in the elderly. These diseases and their effect on the lives of veterans and all Americans motivate much of the research presented here.

Osteoarthritis and Skeletal Regeneration

Approximately 43 million, or one out of every seven, Americans have some form of arthritis. Arthritis is the most prevalent chronic condition among adults over the age of 65 and one out of every two individuals in this age group has severe osteoarthritis in at least one joint. The costs attributable to this disease are staggering, estimated at nearly $65 billion in the U.S in 1992, with about half the cost for medical care and half due to lost wages. Clearly the treatment and prevention of this disease deserve to be a national health care priority.

In the lead article Mikic et al. examine the effect of immobilization on the development of the tibio-femoral meniscus and the tibio-talar sesamoid in an embryonic chick model. With immobilization, the initial meniscal condensation forms, but the meniscus fails to mature and eventually degenerates completely, while the sesamoid fails to form at all. The tibio-talar sesamoid in the chick clearly requires appropriate extrinsic regulatory signaling even for initial development to commence. This study shows that appropriate mechanical stimulation is essential for normal development and immobilization can profoundly affect developmental pathways. Since tissue and organ regeneration is in many ways a recapitulation of development, it is clear that mechanobiological regulation has important implications for designing and optimizing rehabilitation protocols involving tissue engineering and regeneration in adults.

In their article on tendon adaptation Wren et al. propose a simple rule that can account for the fibrocartilaginous metaplasia that occurs in tendons that wrap around bones. In such cases, fibrocartilage develops within the tendon in the region adjacent to the bone. In teleological terms this metaplasia can be thought of a protective mechanism, while mechanistically it can be viewed as a direct response to the local mechanical environment consisting of compressive hydrostatic stresses combined with longitudinal tensile strains. This adaptation is consistent with the development of fibrocartilage that is often seen in the repair of full thickness cartilage defects and thus provides further insight into the challenges of treating osteoarthritis.

Beaupré et al. use theoretical and computational models to show that the mechanobiological principles that guide initial joint development and tendon fibrocartilage metaplasia are the same ones that regulate cartilage thickness throughout life. Their study provides strong evidence that not only is cartilage growth and ossification responsible for the efficient self-design of diarthrodial joints during development, but it also plays a key role in the destruction of articular cartilage in old age. These types of theoretical and computational studies are extremely valuable for guiding the design of new in vitro and in vivo investigations into the prevention and treatment of osteoarthritis.

In many ways the \textit{in vitro} cell culture study of Smith et al. complements and reinforces the findings of the previous computational studies by Beaupré et al. and Wren et al. Smith et al. examine the effects of hydrostatic pressure on the expression of key cartilage matrix constituents including type II collagen and aggrecan. In comparison to unloaded controls, an intermittent loading of 10 MPa at a frequency of 1 Hz for 4 hours per day for 4 days led to a 9-fold increase in mRNA signal for type II collagen and a 20-fold increase in signal for aggrecan. These are two of the major building blocks of healthy cartilage and their synthesis is a prerequisite for normal cartilage development and successful cartilage repair and regeneration. The anabolic effects of hydrostatic pressure
on chondrocyte metabolism suggests that mechanical loading may be an important and perhaps essential ingredient in the repair and regeneration of articular cartilage. Andriacchi et al. describe a new technique for evaluating the progression of osteoarthritis called dynamic functional imaging, which combines high resolution magnetic resonance images (MRI) of articular cartilage with kinematic and dynamic measurements from gait analysis. The purpose of this integrated approach is to determine the location of areas of cartilage damage using MRI and to correlate these locations with the corresponding loads that exist during locomotion and other activities of daily living. The use of dynamic measurements has been shown to have better predictive value of clinical outcome than traditional static measurements and the use of high resolution MRI provides a true three-dimensional map of cartilage integrity. This new technique promises to be a powerful diagnostic tool to identify patients at risk for rapid progression of cartilage loss and to aid the clinician in choosing the most beneficial pharmacological or surgical treatments.

Although current surgical and physical rehabilitation treatments for cartilage repair are not very successful, modern tissue engineering approaches to cartilage regeneration offer great promise. Glowacki provides an excellent review of the state-of-the-art in this area and offers a view into the future including the development of new tissue scaffolds, biological factors, and mechanical protocols for regulating chondrogenesis. As we learn more about the challenges of neochondrogenesis, it becomes clear that the efforts of multi-disciplinary teams with expertise in cell and molecular biology, biomaterials, and bioengineering are needed in order that the successful, long-term repair and regeneration of cartilage may become a clinical reality.

To conclude the section on osteoarthritis O’Driscol and Giori give their perspective on the clinical use of continuous passive motion (CPM) in the prevention of joint stiffness following total knee replacement surgery. The use of CPM is a clear attempt to regulate skeletal biology via mechanical stimulation. O’Driscol and Giori argue that non-adherence to several empirical principles of CPM use is the cause of the negative results that have been reported in the literature. These principles have in large part been empirically determined and considering the fact that widespread clinical use of CPM only began in the 1980’s, optimal clinical protocols and a better understanding of the underlying mechanobiological principles are obvious areas for further investigation.

Osteoporosis and Bone Functional Adaptation

As is the case with arthritis, the prevalence of osteoporosis increases with age. Osteoporosis afflicts an estimated 25 million Americans, and bone fracture is its most serious medical consequence. In particular, hip fracture is a major health concern among the elderly. This year, there are expected to be 350,000 hip fractures in the US. The mortality rate 1 year after a hip fracture is approximately 20 percent, meaning that one out of five individuals sustaining a hip fracture will die within 12 months. Even though genetic factors are responsible for a significant portion of skeletal development, it is estimated that up to 20 percent of bone mass is regulated by controllable factors. We expect that the mechanobiology of bone development, maintenance and adaptation will be key areas of investigation in our efforts to better diagnose, treat and prevent osteoporosis.

In his article on bone adaptation Mosley clearly explains the motivation and necessity for the use of in vivo animal models in the study of the mechanical regulation of bone mass and architecture. Because of the confounding effects of surgery, there is a growing trend for the use of less invasive models. Mosley and colleagues have developed a non-surgical approach for loading the rat ulna that is providing important information about how mechanical stimuli regulate bone biology in both growing and adult animals. Bone adaptation in old animals is clearly relevant to the progression and treatment of osteoporosis in the elderly, while the response in young animals may be one of the keys to prevention, as we see in the following article by van der Meulen et al.

Osteoporosis is a disease associated with aging, however, much of the battle against osteoporosis is waged during adolescence and young adulthood with the acquisition of peak bone mass. In their article on the mechanobiology of femoral neck structure during adolescence van der Meulen et al. show that parameters related to skeletal loading such as overall body mass and lean body mass explain much more of the variance in femoral neck structure and strength than do parameters such as age and pubertal stage. These results suggest that the femur is particularly responsive to skeletal loading during
development and therefore, maximizing bone acquisition during adolescence and young adulthood is one way to reduce the number of osteoporotic fractures later in life.

Investigations into the relationship between skeletal form and functional loading have a long and rich history. Jacobs provides a brief overview of the seminal work since the 19th century, and he discusses some of the important advances of the past decade. The ability to predict bone adaptation using computational models is influencing joint replacement design, improving exercise protocols for osteoporosis prevention, and providing more optimal designs of fracture fixation devices. Inevitable advances in computer capabilities and imaging technologies promise to make these models more realistic and more clinically relevant.

In their article on tendon and ligament adaptation Wren et al. apply some of the same approaches that have proven extremely useful for examining the response of bone to disuse and exercise. These authors demonstrate that fibrous tissue adaptation to immobilization and exercise can also be successfully simulated with computer models. Their study provides a much needed theoretical basis for understanding the results of other investigators and will help to identify potential deficiencies in experimental designs and important parameters that should be monitored in future studies.

The topic of the article by Kiratli et al. is skeletal changes in the lower limbs after spinal cord injury (SCI). These authors point out that bone strength and therefore fracture risk are functions of both material and geometric properties, each of which is regulated by mechanobiology. Their techniques for assessing bone properties apply not only to individuals with SCI, but also to the much larger population of elderly individuals at risk of fractures from osteoporosis. It is obvious that advances in the ability to predict fracture risk in the SCI population can be transferred directly to the elderly, osteoporotic individual as well.

Hernandez et al. introduce a new model for bone adaptation that can account for both mechanobiologic and metabolic factors. Previous investigators have typically considered either mechanobiologic factors or metabolic factors, but not both. In studying osteoporosis, however, it is important to consider both since the progression, treatment and prevention of the disease is so clearly dependent on the combined effects of mechanical and metabolic factors, as the following article by Taaffee and Marcus demonstrates.

It is most appropriate to conclude this single topic issue with the article by Taaffee and Marcus, since the effect of exercise on muscle and bone mass is one of the most obvious manifestations of skeletal tissue mechanobiology. When reading their article one may be struck by the variety of candidate pharmacological agents and exercise protocols available for combating age-related changes in muscle and bone mass. I think it is fair to say that the development of better treatment protocols can only be helped by an improved understanding of skeletal tissue mechanobiology.

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