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## Osteoarthritis – Why Exercise?

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Osteoarthritis (OA) is a degenerative joint disease and a leading cause of adult disability. The etiology of OA is not clear, but common risk factors for developing OA include age, joint injury, mechanical overuse, and obesity. Exercise is the most common non-pharmacologic therapy prescribed to patients with osteoarthritis. The Arthritis Foundation promotes an exercise program involving low-impact physical activity, and participants have reported less pain and fatigue, and increased strength. Clinical trials of patients with OA report physical activities including aerobic exercise, stretching/flexibility, endurance training, aquatic exercise, and muscle strengthening lead to improvements in pain relief, body weight, and metabolic abnormalities [1]. Factors which are critical to successful outcomes of exercise programs include performing exercises at an appropriate intensity and duration, and long-term adherence to exercise programs. Individualized exercise programs are important to educate patients to avoid exercises which may be harmful to injured joints (e.g. high impact activities). Patient monitoring or prescription of exercises which the patients find enjoyable may promote long-term adherence to an exercise program.

In addition to the symptom-modifying effects of exercise, there is evidence of exercise exerting disease-modifying effects. For example, increased physical activity in the form of aerobic and weight-bearing exercises resulted in increased proteoglycan content, one of the major components of the cartilage extracellular matrix, in the cartilage of OA patients [2]. Strength training for 30 months, compared to range of motion exercises alone, resulted in a decreased mean rate of joint space narrowing [3].

Exercise at a moderate intensity is extremely important. Acute or chronic high-intensity loads, which often occur in athletes participating in high-impact sports such as soccer, football, and basketball, may increase risk of developing OA [4–6]. Inadequate loading also creates a degradative response within the articular cartilage [7,8]. Partial weight bearing for 7 weeks leads to cartilage thinning in the knee articular cartilage [9]. Patients with spinal cord injury, who have been subjected to bed rest, exhibit a rate of cartilage atrophy greater than that reported in age-associated osteoarthritis [10]. Exercise at moderate levels will also help avoid joint injuries. Traumatic joint injuries, such as anterior cruciate ligament (ACL) tears, result in degenerative changes in the articular joint such as chondral softening and

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fracture [11,12]. The definition of “moderate exercise” however, remains a challenge. It may be necessary to determine appropriate exercise intensities on an individual basis.

While degradation of the articular cartilage is considered a hallmark of OA, the pathogenesis of this disease includes pathologic changes to tissues of the entire joint, including altered bone remodeling, synovitis, and degeneration of the tendons and ligaments [13]. Targeting only one aspect of the disease process, for example, suppressing bone turnover with risedronate [14], has not been reported to slow progression of OA. Therefore, the design for future OA therapies should consider the influences of all joint tissues. Mechanical loading of an articular joint involves the participation of multiple joint components, including muscles, ligaments and tendons, bone and articular cartilage. The biological effects of mechanical stimuli on these and other joint tissues, such as the synovium, are dependent on the magnitude, duration, and mode of loading.

While the clinical benefit of dynamic moderate exercise is significant, mechanisms underlying the effects of physical activity on the joint are not well understood. Experimental studies in animal models of osteoarthritis and human cartilage tissues *ex vivo* suggest that moderate exercise also leads to increased anti-catabolic, anti-inflammatory, and anabolic activity [15]. Dynamic stimulation of cartilage explants increases synthesis of cartilage matrix components and physiologic loading of animals with experimental osteoarthritis suppresses expression of inflammatory mediators (e.g. interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$ ) and enzymes which directly cleave the articular cartilage including (MMPs) matrix metalloproteinases and ADAMTS (A Disintegrin And metalloproteinase with Thrombospondin motifs) [15].

Exercise is beneficial for the maintenance of metabolic homeostasis. Excessive adipose tissue, as seen in obesity, not only increases mechanical stresses on weight-bearing joints, but also generates an imbalance in the secretory profile of adipokines, including leptin, adiponectin, visfatin, and resistin [16]. These conditions create an environment of low-grade inflammation, which in turn upregulate expression of MMPs and ADAMTS, and eventually cartilage breakdown. A recent clinical trial studied the effect of an intensive 18-month diet and exercise program in 454 overweight and obese patients with osteoarthritis. The exercise program consisted of aerobic walking, strength training, a second aerobic phase, followed by a cool-down period. This diet and exercise regime led to significant reduction in weight, total fat mass, pain relief, and improvements in mobility. Diet and exercise also reduced knee joint loading and plasma levels of inflammatory cytokine interleukin (IL)-6 [17]. These findings suggest that exercise exerts anti-inflammatory and biomechanical beneficial effects on a systemic and local joint tissue level. Recently, moderate treadmill running has also been demonstrated to activate autophagy, a physiologic process of intracellular recycling, in skeletal muscle [18]. Interestingly, pharmacologic activation of autophagy in chondrocytes, in the surgical models of osteoarthritis prevents cartilage degradation [19], suggesting exercise may maintain chondrocyte function by activating autophagy.

Can we design an “exercise pill” to mimic the physiologic effects of exercise on joint tissues? Such treatments will be especially beneficial to astronauts, bed-ridden patients, and patients with very limited mobility due to degenerative joint diseases. Studies suggest

proteins such as integrins and primary cilium, in response to moderate loading, sense mechanical signals and initiate anti-catabolic, anti-inflammatory, and other pathways involved in cartilage homeostasis. The elucidation of these mechanosensitive signaling pathways in joint tissues will reveal specific molecules which may be pharmacologically targeted for novel OA treatments.

In conclusion, dynamic moderate exercise in patients with OA exerts symptom-modifying effects, and may have the potential to exert OA disease-modifying effects. Exercise involves all tissues within the articular joint and may comprehensively target multiple aspects of osteoarthritis progression including the suppression of inflammation and catabolic activity, enhancing anabolic activity, and maintaining metabolic homeostasis. Elucidation of the mechanisms mediating these effects could lead to the development of pharmacological mimics of exercise. These will be especially beneficial to patients with limited joint mobility and may also synergistically enhance the chondroprotective effects of moderate exercise.

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