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REVIEW ARTICLE

Managing the Early Risk of Posttraumatic Osteoarthritis Following Anterior Cruciate Ligament Injury

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Abstract
Approximately, one-third of individuals who sustain an anterior cruciate ligament (ACL) injury and undergo ACL reconstruction develop radiographic posttraumatic osteoarthritis within one decade of injury. Traditional ACL reconstruction and therapeutic rehabilitation do not reduce the risk of developing posttraumatic osteoarthritis compared to individuals who do not elect to undergo ACL reconstruction. Currently, there is no cure for posttraumatic osteoarthritis; therefore, prevention of posttraumatic osteoarthritis following ACL injury and reconstruction is paramount for maintaining long-term joint health following injury. The purpose of the current clinical commentary is to review the overall global burden of knee osteoarthritis and further explain the risk of posttraumatic osteoarthritis following ACL injury and reconstruction, as well as outlining current methods for detecting joint tissue changes that may be indicative of early posttraumatic osteoarthritis following ACL injury. Finally, we review current concepts for managing the risk of posttraumatic osteoarthritis development following ACL injury and reconstruction. The overall goal of the current review is to provide sports medicine clinicians with knowledge to help improve the long-term health of patients with traumatic knee injuries.

Keywords Knee · ACL · PTOA

Introduction

Osteoarthritis is a disease impairing the function of moveable joints (e.g. ankles, knees, hips, and intervertebral joints of the spine) [27]. The disease process can be initiated by multiple microtraumas overtime or an acute macrotrauma to joint tissues, which leads to deleterious changes in joint tissue metabolism resulting in an overall breakdown in the structure of joint tissues [17, 27]. While osteoarthritis is often clinically characterized by a change in articular cartilage health, other tissues such as subchondral bone, meniscus, synovium and ligaments are also affected as osteoarthritis develops within a joint [33]. The pathogenesis of osteoarthritis is one that impacts the entire joint organ and the process may be different between individuals [33] leading to the most current theories that multiple osteoarthritis phenotypes may exist [13]. In the addition to the underlying disease process occurring at the tissue level, patients report disability related to pain, joint stiffness, and loss of physical function which impact an individual's quality of life [62].

Treating osteoarthritis is expensive, as osteoarthritis is one of five medical conditions resulting in a third of all medical costs in the United States annually [6]. Specifically, knee osteoarthritis is the 11th leading cause of disability worldwide [11]. The median age of knee osteoarthritis diagnosis is 55 years old [36], suggesting that many individuals diagnosed with knee osteoarthritis will live multiple decades with disability. Additionally, individuals with symptomatic knee osteoarthritis are at a 23% increased risk of premature death compared to those without knee osteoarthritis after controlling for age, sex, and race, which has led experts to consider osteoarthritis a serious disease that impacts both quality of life and is related to life expectancy [21]. Multiple risk factors at the individual (e.g. age, sex, obesity, and race), and specific joint level (e.g. joint injury, limb alignment, occupation, strength of surrounding musculature) are related to the onset of osteoarthritis [39]. The purpose of this review is to outline the risk of developing knee osteoarthritis following an anterior cruciate ligament (ACL) injury, as well

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as methods for detection of early knee osteoarthritis and approaches for managing the risk of developing future posttraumatic osteoarthritis (PTOA) following an ACL injury.

Posttraumatic Osteoarthritis

The development of osteoarthritis specifically following an acute joint injury is termed posttraumatic osteoarthritis. It is estimated that between 12% [8] and 35% [9] of all knee osteoarthritis cases occur following a traumatic knee injury. Knee injury is most common between the ages of 16 and 24 [40], suggesting that individuals who develop PTOA may do so earlier in life compared to those with idiopathic knee osteoarthritis (i.e. primary osteoarthritis not resulting from a known injury). Individuals with PTOA often demonstrate more disability than those with idiopathic knee osteoarthritis, as younger individuals may develop PTOA earlier in life when they desire more active lifestyles compared to older individuals who more commonly develop idiopathic osteoarthritis phenotypes [1]. Additionally, individuals with PTOA often report worse outcomes following knee joint replacement, suggesting long-term osteoarthritis outcomes may be worse in those who develop PTOA. Overall, PTOA patients present differently than individuals with idiopathic knee osteoarthritis and specialized therapeutic approaches should be developed and implemented to treat individuals at risk for PTOA onset or progression. Individuals who sustain an ACL injury are at high risk for developing PTOA [34]; yet, current clinical practices often focus on returning individuals to sport participation while little emphasis is directed to maintain long-term joint health and decreasing PTOA onset. Therefore, an opportunity exists to substantially improve the care of ACL injured patients by understanding PTOA risk and properly managing that risk early following injury.

Linking Posttraumatic Osteoarthritis and Anterior Cruciate Ligament Injury

In the United States, males demonstrate an overall higher incidence (81.7 per 100,000) of ACL injuries compared to females (55.3 per 100,000) [54], which may be due to the overall all greater lower extremity injury risk associated with male-dominated sports, such as American Football. In sports where males and females demonstrate similar levels of participation (e.g. soccer and basketball), females demonstrate greater incidence rates compared to males [54]. Interestingly, females (14–18 years old) demonstrate their highest ACL injury incidence rates at younger ages compared to males (19–25 years old) [55]. In a population study from the United States, approximately 75% of individuals with an ACL injury elected to undergo ACL reconstruction (ACLR) and approximately 98% of individuals with an ACL injury under 18 years of age elected to undergo ACLR [54]. Approximately, 82% of individuals who undergo ACLR return to some level of physical activity and 63% of individuals with an ACLR return to pre-injury levels of physical activity status [2]. Approximately, 7% of individuals who undergo ACLR will sustain a second ACL injury on the ACLR limb and 8% will sustain a new injury on the contralateral uninjured limb [61]. Therefore, ACL injuries are common in young physically active individuals and understanding the lasting impact of this injury is critical for maintaining long-term quality of life in ACL injured patients.

One of the most devasting risks of ACL injury is the long-term impact the injury has on the health of the joint. Approximately, one-third of individuals with an ACL injury will demonstrate radiographic PTOA within the first decade of ACL injury regardless of undergoing ACLR or remaining ACL deficient [34]. Approximately 50% of individuals will demonstrate PTOA by the second decade following ACL injury and ACLR [34]. These data indicate that individuals with an ACL injury are at high risk of developing PTOA, and this risk is not mitigated by undergoing traditional surgical ACLR and therapeutic rehabilitation. Therefore, a large proportion of individuals who sustain ACL injuries early in life may develop PTOA in their 30's and live many years with PTOA-related disability. In order to prevent PTOA in individuals with an ACL injury it is important to develop novel methods for detecting deleterious joint tissue changes early following ACL injury [43]. Furthermore, it is critical for clinicians to be able to manage the risk of PTOA early following the initial injury.

Early Detection of Posttraumatic Osteoarthritis-Related Changes Following ACL Injury

Traditionally, knee osteoarthritis is clinically diagnosed using plain radiographs (i.e. X-ray) and the severity of knee osteoarthritis is assessed by evaluating the presence of osteophytes and tibiofemoral joint space narrowing [26]. Unfortunately, biological changes to knee joint tissues occur prior to gross structural joint changes that are able to be identified using radiographs. Thereby, the use of radiographs may not be a sensitive enough measure to determine the early changes related to development of PTOA. Additionally, by the time radiographic changes are detectable, a substantial change in joint structure has occurred and reversal of these joint tissue changes is not possible with current treatments. Therefore, in order to treat PTOA prior to significant structural joint degeneration, it is critical to detect changes in joint health early in the disease process. New research using biochemical markers from synovial fluid, as well as serum

and plasma has sought to understand changes in joint tissue metabolism prior to radiographic onset [17]. Increases in multiple biochemical markers, including markers associated with joint inflammation, and cartilage breakdown, have been reported following injury [17]; yet, a biochemical marker from synovial fluid or blood that would predict PTOA onset following ACL injury has not been determined.

Magnetic Resonance Imaging for Assessing Early Posttraumatic Osteoarthritis Changes

Novel magnetic resonance imaging (MRI) techniques have been utilized to track changes in joint tissues following ACL injury and ACLR, which has led to a better understanding of disease progression and detection of PTOA development. The development of traumatic bone marrow edema-like lesions on the lateral condyle of the femur occur in approximately 63% of individuals who sustain an ACL injury [16, 63]. While bone marrow edema-like lesions resolve in 38% of individuals within the first 3 months following ACL injury [16], new atraumatic bone marrow edema-like lesions have been detected in 21 out of 47 studied injured knees at 2 years following ACL injury [15]. Therefore, early changes in subchondral bone health occurs at the time of ACL injury and these changes may continue during the first 2 years in a proportion of individuals following ACLR. Further these initial traumatic bone marrow edema-like lesions are associated with the development of harmful changes in cartilage composition [7]. Specifically, decreased proteoglycan density in the femoral articular cartilage is associated with the progression of osteoarthritis [52, 60]. Novel compositional MRI techniques, using T1ρ relaxation times that are sensitive to proteoglycan density of the articular cartilage, have detected in vivo decreases in femoral articular cartilage proteoglycan density at 1 and 2 years following ACLR [31, 49, 56]. These changes in T1ρ MRI relaxation times suggest that early changes related to PTOA development occurs within the first 12 months following ACL injury. During the first two years following ACLR other MRI studies have demonstrating an increase in femoral cartilage thickness [15], while cartilage thinning has been found between an average of 3.7 years post-ACLR [3]. These data suggest that early cartilage thickening may predate the eventual cartilage thinning occurring later in the PTOA disease process. While the pathophysiology leading to a "thickening-to-thinning" cartilage response remain unknown, it has been hypothesized that change in cartilage composition may draw water into the cartilage resulting in a swelling of the cartilage tissue [20]. Further MRI research evaluating joint morphology has demonstrated changes in the shape or curvature of the femur and tibia within the first 5 years following ACL injury [25], providing evidence that significant changes to anatomical features occurs within the first 5 years following injury, which may be associated with the eventual development of PTOA. While the novel MRI findings have provided critical information regarding the early pathogenesis of PTOA, more research is needed to link these changes to future PTOA development and radiographic changes that may determine how best to use early MRI to determine PTOA onset.

While MRI is an important tool for visualizing joint related changes associated with PTOA development, MRI can be expensive and difficult to access for many ACL patients. Diagnostic ultrasound has been used to reliability visualize changes in femoral cartilage thickness and cross-sectional area [19]. Greater femoral cross-sectional area, detected with diagnostic ultrasound, has been reported in patients with an ACLR [20], thus agreeing with data from other MRI studies [15]. Additionally, diagnostic ultrasound measures of femoral cartilage cross-sectional area is capable of evaluating the immediate response of the femoral cartilage to loading following walking, running, or jumping [18, 19], suggesting that diagnostic ultrasound may provide a means for determining how cartilage responds to joint loading. While diagnostic ultrasound may provide more accessible and cost-effective assessments of femoral cartilage, it is limited to evaluating articular cartilage in only certain regions of the femur [18–20] and future research is needed to determine if therapeutic ultrasound measures relate to PTOA development.

Recent research has evaluated habitual, or self-selected, walking speed as a potential indicator of PTOA development. An individual's habitual walking speed typically remains stable throughout the first 6–7 decades of life [24] and a decrease in walking speed has been linked to the development idiopathic knee osteoarthritis [22, 51]. Recent data suggests that slower habitual walking speeds at 6 months post ACLR are associated with greater T1ρ MRI relaxation times (i.e. lesser proteoglycan density) at 12 months following ACLR [41]. Additionally, slower walking speeds in a cohort of ACLR patients, at an average of 43 months post-ACLR, demonstrated greater serum biomarker concentrations of type II cartilage breakdown [46]. These data suggest that monitoring habitual walking speed following ACLR may be an important clinical marker of PTOA development. Finally, monitoring patient-reported function should play an important role in determining which patients may be at heightened risk for developing PTOA. Previous studies have demonstrated that approximately 40% of individuals demonstrate clinically relevant knee symptoms at 2 and 6 years following ACLR [59], which is similar to the percentage of individuals who will develop PTOA in the first decade following ACLR [34]. Additionally, worse patient-reported function is associated with greater T1ρ MRI relaxation times (i.e. lesser proteoglycan density) at 12 months following ACLR [49], suggesting that individuals with worse joint tissue health early following ACLR will also self-report

worse function. Therefore, monitoring patient-reported function with valid and reliable measurement tools such, as the Knee injury and Osteoarthritis Outcomes Scale [53] or the International Knee Documentation Committee Index [23], may be able to alert clinicians to patients who are demonstrating early deleterious knee joint changes consistent with PTOA development.

Managing Posttraumatic Osteoarthritis

There is no current cure for PTOA, therefore prevention of PTOA is critical following ACLR. While primary prevention of an initial ACL injury is the best method for preventing PTOA onset, secondary prevention of PTOA early after an ACL injury is critical for optimizing long-term health of ACL injured patients. While guidelines for managing idiopathic osteoarthritis have been published [38], there is a lack of best-practice guidelines for PTOA prevention. There is emerging data within the literature regarding practices that may help manage the risk of PTOA risk following knee injury.

Education and Serial Assessment of Patients

Education of both clinicians and patients regarding the risk of PTOA following ACL injury and ACLR is paramount for mitigating the burden of PTOA. A recent survey of certified athletic trainers who treat patients with ACL injury and ACLR demonstrated lack of knowledge regarding the pathogenesis of PTOA following ACLR [47], as well as indicating a perception among sports medicine clinicians that the development of PTOA in an ACLR patient would not be a serious health concern [47]. In this 2017 survey certified athletic trainers tended to underestimate the prevalence of PTOA in the first decade following ACLR and overestimate the ability of traditional ACLR and therapeutic rehabilitation to effectively prevent PTOA [47]. Similarly in a related study of ACLR patients, only 27% of ACL injured patients discussed the development of PTOA with their healthcare providers and approximately two-thirds of ACL injured patients who elected to undergo ACLR believed that ACLR would decrease their risk of PTOA [5]. Additionally, the majority of individuals with an ACLR did not believe developing osteoarthritis would be a major healthcare concern [5]. Therefore, education regarding the risk of PTOA following ACL injury should be implemented for healthcare professionals as well as for ACL injured patients. Education of the patient should be implemented by different clinicians, ensuring that different providers do not assume that PTOA education is another provider's responsibility. It is also critical for clinicians to serially assess their patients following ACL injury and after secession of formalized rehabilitation as knowledge of the progression of their symptoms and functional status is critical following return to unrestricted physical activity.

Improving Strength and Proper Movement Biomechanics

Persistent lower extremity muscle weakness is common following ACL injury and ACLR [57]. Quadriceps weakness is associated with changes in T1ρ MRI relaxation times at 6 months following ACLR [50] and with radiographic tibiofemoral joint space narrowing at 4 years following ACLR [58]. Greater quadriceps strength following ACLR is associated with better patient-reported function [45, 44] and may be associated with more optimal gait biomechanics. It is hypothesized that diminished quadriceps strength is associated with lesser knee flexion excursions during gait, which may cause aberrant compressive forces at the knee throughout the stance phase of gait [30]. For this reason, proper quadriceps strengthening and targeted gait retraining are needed to ensure that individuals properly attenuate forces at the joint following ACLR.

Activity Modification

Proper loading of the tibiofemoral joint is important for maintaining optimal joint health. Both excessive and insufficient joint loading can cause deleterious changes to joint tissue health [28, 42]. Therefore, it is important that individuals engage in safe exercise and physical activity in order to decrease the risk of osteoarthritis. Overall, participation in most types of athletics has not been found to increase the odds of developing knee OA [14]. Certain sports are associated with increased odds of developing knee osteoarthritis including, elite-level long-distance running (OR = 3.3), competitive weightlifting (OR = 6.9), and wrestling (OR = 3.8) [14]. Engaging in exercise can be safe and is important for overall wellness. In individuals with knee osteoarthritis, habitual running does not increase osteoarthritis progression, suggesting that individuals could continue to exercise without incurring increased risk of knee osteoarthritis progression [10, 32]. Conversely, returning to activities associated with a high risk of sustaining a subsequent knee injury may increase the risk of hastening osteoarthritis disease progression. In a recent study of retired National Football League players, the history of a knee injury was associated with increased odds of undergoing knee replacement [12], which is a treatment for end-stage knee osteoarthritis. Individuals with 3 or more injuries were at significantly greater odds of undergoing a knee replacement compared to individuals with one knee injury. These data suggest that patients who have sustained 2 knee injuries should consider limiting engagement in activity that may increase the risk for

a third knee injury as a third knee injury would significantly heighten the risk of developing end-stage knee osteoarthritis.

Maintaining an Optimal Body Weight Index

High body mass index (BMI) is one of the most predictive risk factors for idiopathic knee osteoarthritis [64]. It has been estimated that an increase of 10 lbs in body weight is equal to approximately 30-60 lbs of force at the knee [35]. It is also hypothesized that high amounts of adipose tissue may increase systematic circulating adipokines, which may increase inflammation throughout the body, thereby hastening joint damage in multiple weight bearing and non-weight bearing joints [4]. Knee injury is often coupled with weight gain, which may be caused by a decrease in physical activity following injury [37]. It is not clear if BMI has a direct association with patient-reported function following ACLR; yet there is some evidence to suggest that individuals considered overweight or obese (≥ 25 BMI) are less likely to achieve population average physical function scores compared to individuals who are considered normal or low BMI (<25) [48]. Conversely, greater BMI does have an association with increased type II collagen breakdown in females with an ACLR [29], suggesting that high BMI may impact both patient-reported function and deleterious biological joint tissue changes following ACL injury. Therefore, it is critical to maintain an optimal BMI following injury in an effort to prolong joint health and overall wellness.

Conclusion

Knee osteoarthritis is a serious health concern that limits physical function and quality of life. Individuals who sustain an ACL injury are at high risk of developing PTOA. There is no current cure for PTOA; therefore, prevention of PTOA following injury is critical for long-term joint health. Sports medicine clinicians must understand the risk of PTOA in patients who have sustained a knee injury and specifically take early steps to detect and manage the development of the disease.

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