OSTEOARTHRITIS

Does post-injury ACL reconstruction prevent future OA?

Chunyi Wen and L. Stefan Lohmander

Young adults with an acute rupture of the anterior cruciate ligament of the knee are faced with the decision of whether or not to undergo early reconstructive surgery. However, a lack of high-quality evidence means questions remain about whether this surgical strategy protects against the development of osteoarthritis in the future.

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Return to an active lifestyle and risk of future osteoarthritis (OA) are two, sometimes conflicting, concerns of the young adult with an acute rupture of the anterior cruciate ligament (ACL) of the knee. These concerns could influence the decision of whether or not to undergo early surgery to reconstruct the torn ligament. Brophy and colleagues recently reported the results of a retrospective study of the prevalence of previous knee surgery, such as ACL reconstruction and meniscectomy, in an arthroplasty registry of 1,286 patients with a diagnosis of late-stage OA or post-traumatic arthritis.[1] Strikingly, they found that patients with a history of ACL reconstruction underwent knee replacement at ~50 years of age, compared with age ~67 years for those without a history of knee surgery. With knee replacement at a young age markedly increasing the risk of revision surgery, the results of the study by Brophy *et al.*[1] highlight the problem of OA resulting from knee injury, and raise the question of whether we can prevent this serious, late sequel.

The rate of radiographic OA after ACL rupture and reconstruction varies widely between reports, with a crude estimate of 50% at about 15 years after injury.[2] This high rate of radiographic signs of OA has remained unchanged despite refinements to surgical reconstruction techniques.[2]

The patient-reported outcome of an ACL rupture and reconstruction is influenced by patient-related factors such as sex, BMI, smoking status, pre-surgery physical activity, whether the patient returns to playing sports and the patient's expectations (Figure 1). Trauma-related factors, such as concomitant injuries to the meniscus or joint cartilage, are also highly relevant.[3] The only recent randomized controlled trial (RCT) to compare early ACL reconstruction plus structured rehabilitation with rehabilitation alone failed to show a difference between patient-reported outcomes of the two strategies at 2 or 5 years,[4,5] suggesting that many patients do as well for at least 5 years without undergoing early surgical reconstruction. Furthermore, no high-level evidence exists to support a protective effect of ACL reconstruction against later development of OA. On the contrary, an RCT comparing early reconstruction and structured rehabilitation found no difference in the rate of radiographic or clinical signs of OA 5 years after the injury.[5]

The development of OA after an ACL rupture and reconstructive surgery remains an unsolved problem. To better understand the role of patient-related and injury-related factors in the choice of treatment and in the outcome, we need large and long-term prospective cohort studies that include those treated with and without ACL reconstruction, to complement additional RCTs comparing the efficacy of different interventions.

We also need further basic research to understand the role of the immediate joint trauma at the time of the ACL rupture in the development of OA, as well as the relative contribution of long-term chronic derangement of joint loading. Chondral injury and bone contusion is present in almost all patients with acute traumatic ACL rupture.[6] This immediate mechanical insult activates inflammatory cytokine and protease cascades in cartilage, synovial and bone cells, and triggers apoptosis and catabolic responses in the articular cartilage that degrade the cartilage matrix.[7] These processes release matrix fragments that can function as damage-associated molecular

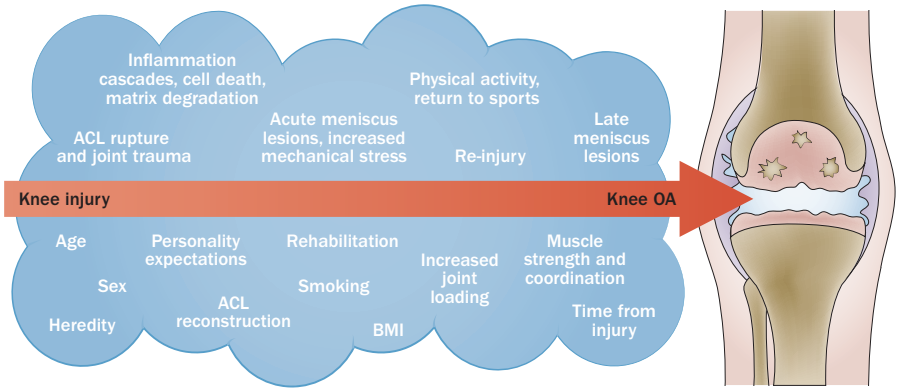

Figure 1 | Development of OA after acute rupture of the ACL of the knee. OA following ACL rupture is the consequence of the interaction of many risk factors, some associated with the person, such as heritability, and others with the environment, such as the severity of the trauma. Evidence that current interventions are able to alter the course from ACL rupture to OA is lacking. Reprinted by permission of SAGE Publications from Lohmander, L. S. *et al. Am. J. Sports Med.* **35**, 1756–1769 (2007), © 2007 by American Orthopaedic Society for Sports Medicine. Abbreviations: ACL, anterior cruciate ligament; OA, osteoarthritis.

patterns (DAMPs) and activate Toll-like receptors (TLRs), potentially prolonging the inflammatory response. The possibility needs to be considered that surgery in this acute phase adds an additional trauma that might exacerbate the early-phase pathological processes and extend the joint damage; to replace a torn ACL, bone tunnels are drilled for the tendon graft, resulting in stress deprivation and substantial bone loss.[8] This intervention might compromise not only graft fixation but also the long-term outcome.

The loading patterns of the knee with a ruptured ACL, whether reconstructed or not, are not normal, with increased mechanical load on the cartilage and altered location of the load on the joint surfaces.[9] A damaged meniscus will further enhance this abnormal loading. Joint cartilage with an impaired matrix, such as occurs soon after injury, is most sensitive to increased loading.[10] Recognizing this consequence of injury is important for planning the rehabilitation and physical activity counselling for patients with these injuries.

These early consequences of ACL rupture suggest that, in order to rectify the continued high rate of OA following ACL rupture, we need to direct our attention to the acute phase after injury. We need to explore if early interventions to decrease cartilage cell death, harness inflammatory cascades, prevent activation of TLRs or slow the breakdown of cartilage matrix could prevent or decrease some of the downstream, late consequences of these common injuries. To save the acutely injured joint, we might, in the future, need the same attitudes and urgent actions as now exercised when trying to save myocardium or brain cells in patients with acute infarction or stroke, respectively.

The clinical management of the young active person with OA from a previous knee injury remains a challenge. A structured, personalized exercise program should be the basic and primary approach, together with advice and support to maintain a normal body weight. Patients should be encouraged to continue being physically active, but to avoid high-impact, pivoting activities. Intermittent use of analgesics or a brace might be helpful for some patients. Knee replacement can be effective for those with severe symptoms of OA, and should be considered before they have lost too much function and become deconditioned. The long-term risk of implant revision surgery remains a concern for those who undergo knee replacement at a young age.

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Competing interests
The authors declare no competing interests.

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THERAPY

Oral or subcutaneous methotrexate for rheumatoid arthritis?

Sabri Alsaeedi and Edward C. Keystone

Although methotrexate is the main therapy for rheumatoid arthritis, surprisingly little is known about the optimal route of administration; bioavailability of methotrexate has been shown to vary accordingly. In terms of delaying a switch to biologic therapy, is the subcutaneous route superior to oral methotrexate therapy?

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Methotrexate is the mainstay of therapy for the treatment of rheumatoid arthritis (RA) and a number of other inflammatory disorders. It is usually administered orally, but can be given subcutaneously or by intramuscular injection. As there is a paucity of data with respect to the use of methotrexate in patients with RA in routine care in the USA, Curtis *et al.*[1] examined its use among those patients initiating methotrexate therapy, whether given orally or subcutaneously.

The authors examined the sustainability of methotrexate therapy, as well as the effectiveness of adding another nonbiologic DMARD or switching from oral to subcutaneous methotrexate, on the likelihood of initiating biologic therapy. Patients enrolled in one of two different health insurance programs were evaluated, either Medicare (2002–2011) or commercial health plans provided by a national health insurer (2005–2012). Use of methotrexate, other nonbiologic DMARDS and biologic agents was identified using national drug codes for pharmacy-dispensed medications or the Healthcare Common Procedure Coding System (HCPCS) for medications received from physicians or hospitals.

The results of this study showed that the most common doses of methotrexate were between 10 mg and 15 mg per week, and titration to 20 mg per week occurred in only 45–54% of patients. In patients initiating biologic therapy, more than one-third did