3 The Arthritis Barrier: Long-Term Effects of ACL Trauma on Knee Joint Health

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3.1 Epidemiology of Post-Traumatic Osteoarthritis Following ACL Trauma

The knee joint is a common location of osteoarthritis (OA). As Lohmander et al. explain, "Osteoarthritis describes a common, age-related, heterogeneous group of disorders characterized by focal areas of loss of articular cartilage in synovial joints associated with varying degrees of osteophyte formation, subchondral bone change, and synovitis" [1]. In OA, cartilage undergoes gradual proteolytic degradation of matrix, with increased synthesis of matrix components by chondrocytes. Early in the disease process, cartilage swelling, surface fibrillation, and cleft formation occur, and in later stages, cartilage volume loss appears [1]. In advanced stages, plain radiographs can detect structural changes such as joint space loss, osteophytes, subchondral sclerosis, and bone cysts [1]. Since OA is an insidious disease, early radiographic-based structural changes are often evident long before any clinical symptoms are present and are not necessarily associated with symptoms or functional abilities [1, 2]. Recent advancements in magnetic resonance imaging (MRI) technologies have enabled the assessment of cartilage, meniscus, synovium, and bone in detail and feature earlier detection of the disease process than the use of radiographs alone. For example, MRI can be used to measure the change in articular cartilage thickness, progression of bone marrow lesions, synovial changes, capsule thickening, meniscus maceration, and extrusion [1]. MRI-based T1ρ and T2 relaxation times can be applied to study early cartilage degeneration in advance of radiographic changes [3]. T1ρ relaxation time correlates with the articular cartilage proteoglycan content and T2 relaxation time correlates with the collagen structure and water content such that higher relaxation times indicate worse cartilage matrix health [4–6]. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) is another MRI-based measurement technique that detects cartilage degeneration by estimating the glycosaminoglycans (GAGs) content, which are negatively charged molecules that attach to the matrix protein aggrecan and regulate the Donian osmotic gradient that attracts water into the articular cartilage, the primary cartilage matrix component that provides efficient transmission of contact stress across the knee joint [6, 7]. Shorter T1Gd correlates with lower cartilage GAG content, indicating decreased cartilage health [7]. Of note, radiographic measurement of tibiofemoral joint space loss and MRI-based measurement of tibiofemoral cartilage thickness are not correlated,

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and these two methods of examining changes associated with the onset and early progression of OA should not be used interchangeably [8].

Symptomatic post-traumatic osteoarthritis (PTOA) represents a subset of OA and is a substantial burden to society, as it is estimated that PTOA accounts for 12% of OA cases (12.7 million people), costing the healthcare system an estimated 3 billion dollars annually [9]. Trauma to the anterior cruciate ligament (ACL), menisci, or dislocation of the patella are the most common injuries that place individuals at increased risk of developing PTOA about the knee. The reported prevalence of knee PTOA following ACL trauma varies widely between studies due to many significant variables affecting its development, including the time from injury to follow-up, concomitant injuries, the delay between injury and treatment, the type of treatment, activity level at the time of return to sport (RTS) and preinjury activities, and heterogeneous diagnostic criteria used to characterize the disease. For example, Lohmander et al. reported that 10–90% of ACL-injured subjects have evidence of PTOA at follow-up intervals that ranged between 10 and 20 years after the index injury [1]. A meta-analysis by Ajuied et al. reported ACL injury to be associated with a 3.89 relative risk (RR) of developing any PTOA and a 3.64 RR of developing moderate or severe PTOA (assessed using Kellgren and Lawrence classification or radiographs) at a mean follow-up interval of 10 years [10]. The factors associated with the increased risk of developing PTOA after ACL injury include increased body mass index (BMI) [11–14], female sex [12, 15], increased age [15], smoking [12, 13], and lower education level [12]. Another potential risk factor may be genetic predisposition to the early onset of PTOA. For example, two studies have linked hand OA with increased frequency and severity of knee OA after meniscectomy [16, 17] suggesting that there may be genetic factors involved with the onset and progression of disease following meniscus surgery. In contrast, a more recent study that focused on ACL-injured patients did not find a relationship between the hand OA and knee OA rates [18]. At the current point in time, it is unclear if and how genetics are involved with the development of PTOA following ACL injury.

3.2 Effect of Sport on PTOA Following ACL Trauma

Because the knees of athletes that compete at high levels are exposed to elevated contact stress levels in comparison to the general population's, many studies have attempted to understand the PTOA rates in an athlete or sport-specific manner. One systematic review revealed OA rates, irrespective of the cause, to be 30% of former athletes [19]. Another systematic review by Driban et al. reported between three and seven times higher prevalence of OA in athletes that participate in soccer, elite long-distance running, weightlifting, and wrestling (prevalence ranging 4.2–8.5%) compared with nonsports participants (prevalence ranging 1.3–2.3%). Elite-level basketball, boxing, shooting, and track and field did not have a higher prevalence of OA compared with nonsports participants; however, these findings do not consider joint injury history [20]. Driban et al.'s review also found that joint injury may be the main cause of the high rates of OA in athletes that take part in soccer and ice hockey [20]. A study of elite football athletes participating in the National Football League (NFL) Combine (age range, 20–26 years) reported a 15% prevalence of OA based on MRI or radiographic imaging, and this correlated with prior ACL injury, knee surgery, and increased BMI [21]. The high ACL injury rates in these sports, along with the high stress demands placed on the knee could combine to increase the risk of OA in athletes. Two landmark studies demonstrated 51% of female soccer players (mean age, 31 years) and 41% of male soccer players (mean age, 38 years) had radiographic PTOA 12–14 years after ACL injury, with 80% showing radiographic features of OA in both groups [22, 23]. Simon et al. revealed PTOA rates to be 76.7% in former Division I collegiate athletes (age range, 40–65 years) who had a knee injury requiring surgery during their collegiate career

[24]. In comparison, Losina et al. reported the overall prevalence of symptomatic OA in the general population aged 45–54 years old to be 3.61% for nonobese men and 4.26% for nonobese women [25]. In addition to increased joint stresses and injuries that athletes experience, there are other risk factors that may be linked to high OA rates. For example, Madaleno et al. suggest that the high prevalence of former athletes becoming overweight after retiring could raise OA risk because increased BMI is the risk factor for PTOA [19]. The increased prevalence of OA in the athlete population, especially PTOA, is significant as the studies discussed show that these athletes with OA are often young. The estimated mean age at diagnosis of OA for the general population is 53.5 years [25]. Since athletes may be at risk of experiencing OA at younger ages than the general population, this may have important economic, medical, and quality-of-life implications to consider.

3.3 Effect of ACL Injury and Concomitant Articular Cartilage Injury on PTOA

It is relatively rare that ACL trauma occurs in isolation as it is often accompanied by injury to other structures about the knee such as articular cartilage lesions (46% prevalence), traumatic bone marrow lesions (80% prevalence), meniscus tears (60–75% prevalence), and other ligament tears (5–24% prevalence) [26–33]. This creates a considerable clinical concern because ACL injury combined with trauma to the other structures about the knee significantly increases the risk of developing PTOA in comparison to ACL injury in isolation [1, 34]. Indeed, Risberg et al. revealed that subjects who have suffered ACL injury and undergone reconstruction should not be considered as a homogeneous group because those suffering ACL trauma in combination with injury to other articular and meniscal cartilage structures undergo progression to radiographic and symptomatic PTOA at a much faster rate than those without concomitant injury [34]. This is an important concern because at the time of ACL reconstruction, the patient age, surgical delay, and sex are independently associated with the frequency and location of articular cartilage injury, an early harbinger of PTOA [34, 35]. For example, Keays et al. reported that chondral damage is a strong predictor of future development of tibiofemoral PTOA following ACL reconstruction [36], and articular cartilage abnormalities at the time of ACL injury are associated with worse results and patient-reported outcomes at 2- and 6-year follow-up intervals [12, 13]. Slauterbeck et al. reported patients that are ≥25 years of age at the time of ACL reconstructions are more likely to have multiple articular cartilage lesions throughout the knee (7.7% compared with 1.3% for those <25 years of age) and present with more isolated medial femoral condyle lesions (24.2% compared with 13.3%) [35]. Further, at the time of ACL reconstruction, female patients have a greater proportion of grade 1 articular cartilage lesions of the medial femoral condyle (29% compared with 16% for the males), while male patients have a greater proportion of grade 3 and 4 cartilage lesions of the medial femoral condyle (49% compared with 35% for the females) [35]. Patients that are ≥35 years of age at the time of ACL reconstruction have femoral articular cartilage lesions located more frequently on the medial side in comparison to those <35 years of age [35].

It is important to appreciate that ACL trauma not only has an immediate effect on the knee regarding PTBMLs, but it also affects articular cartilage structure in terms of thickening and thinning of the articular cartilage [37]. Argentieri et al. reported that ACL-injured females had significant changes in articular cartilage thickness in the injured knee compared to the uninjured knee at a median of 15 days post injury, with an increased thickness in the central region of the medial tibial cartilage and thinning of the medial posterior cartilage region (Fig. 3.1) [37]. The medial central areas of increased thickness may indicate acute loss of proteoglycans from the cartilage caused by blunt impact forces, resulting in a shift in water content [37]. The medial posterior areas of cartilage thinning may be the result of injury causing increased contact stress

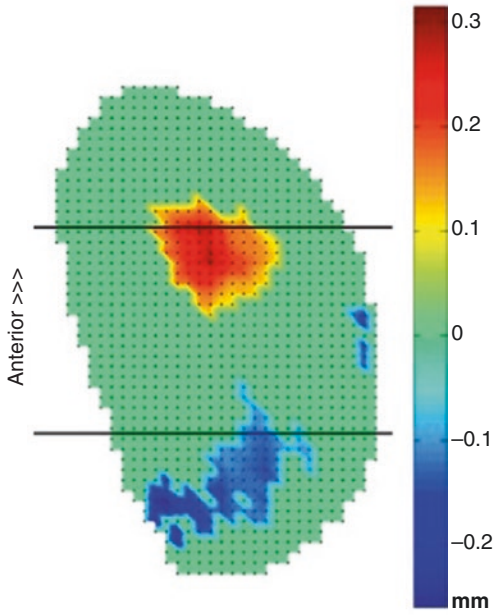

Fig. 3.1 Significant injured-to-uninjured side differences in articular cartilage thickness found in the medial compartment within ACL-injured females. Articular cartilage was thicker in the central region and thinner in the posterior region of ACL-injured knees (From Argentieri et al. [37])

in this region that does not have the material and structural properties of the cartilage normally suited to support such contact stress [37].

3.4 Effect of ACL Injury and Post-Traumatic Bone Marrow Lesions on PTOA

Another common concomitant injury seen with ACL disruption is post-traumatic bone marrow lesions (PTBMLs). These occur at the locations of high-impact forces between the tibial and femoral articular surfaces at the time of an ACL tear [38] and are thought to be associated with edema, hemorrhage, and trabecular microfractures [39–41]. Sievanen et al. used dual-energy X-ray absorptiometry to study the change in periarticular bone about the knee and revealed rapid decreases of bone mineral density soon after an ACL disruption, followed by a phase of partial recovery [42]. Although the independent effects of ACL disruption and ACL reconstruction on bone mineral density and mass are not well understood, reduced bone mass in the injured knee following ACL tears has been shown to exist up to 8 years after the index ACL injury [43–46]. Frobell et al. reported a high prevalence of cortical depression fractures associated with larger PTBMLs and hypothesized this may have been produced by the articular cartilage and subchondral bone experiencing high magnitudes of compressive and shear stress at the time of ACL disruption [47]. These larger PTBMLs are primarily located in the lateral compartment [47, 48]. The presence of PTBML can help indicate the overall mechanism of injury, showing where the joint surface experienced significant compressive and shear forces from the impact of loading at the time of ACL disruption [1, 38]. The large magnitudes of compressive and shear forces transmitted across the tibiofemoral joint at the time of ACL injury have the potential to harm the articular and meniscal cartilage leading to cartilage matrix disruption, accelerated chondrocyte senescence, chondrocyte death, and cell metabolism changes [1, 49, 50]. In addition, Coughlin et al. proposed that bone–cartilage crosstalk, via molecular signaling, changes after a PTBML with subsequent increases in bone remodeling [51]. Changes in the bone–cartilage crosstalk may result in damage to the cartilage and is a potential mechanism for progression to PTOA [51].

A series of studies have found evidence linking PTBMLs with longitudinal cartilage damage. For example, Koster et al. reported bone marrow edema after knee trauma was a strong predictor of PTOA changes to the tibiofemoral joint at 1 year follow-up [52]. Theologis et al. reported the cartilage overlying bone marrow edema-like lesions in the lateral tibia had elevated T1ρ times at 1 year follow-up [53]. Similarly, Gong et al. reported that bone marrow edema-like lesions following ACL injury were associated with higher T1ρ and T2 relaxation times at 2 year follow-up, indicating worse cartilage health [54]. These cartilage changes remained present even after the bone marrow edema-like lesions had resolved, suggesting that damage to cartilage

overlying PTBMLs may be irreversible [53, 54]. Although most PTBMLs resolve within 2 years after ACL injury, Frobell et al. theorized the high magnitudes of compressive and shear forces sustained by the bone and cartilage at the time of ACL injury, as indicated by a PTBML, could initiate biological developments that lead to PTOA in the long term [55]. Evidence suggests that PTBMLs may have a significant role in the mechanism of onset and progression of PTOA following ACL injury. As such, efforts to diagnose and study them in conjunction with ACL injuries and PTOA will be important in future research.

3.5 Effect of ACL Disruption and Concomitant Meniscal Injury on PTOA

Concomitant meniscal damage at the time of ACL injury significantly increases the risk of developing PTOA in the future, particularly in patients that undergo meniscectomy [11, 14, 21, 36, 56–59]. Oiestad et al. reported the prevalence of PTOA ranged from 21 to 48% in those with meniscal injuries compared with 0–13% in those with isolated ACL injuries without meniscal injuries 10 years after the index trauma [58]. In a subsequent study, Oiestad et al. reported 80% of subjects with PTOA had combined meniscal and ACL injuries compared with 62% of subjects with isolated ACL injuries at 10–15 years follow-up; however, there was no significant difference between the groups in terms of their functions and symptoms [60]. Further, after 20 years, PTOA was found in 81% of patients who underwent meniscectomy combined with ACL injury compared with 54% of those who only had isolated ACL injury [18].

Spindler et al. and Jones et al. have revealed that meniscal damage at the time of ACL injury is a risk factor for the development of PTOA and is also associated with worse results and patient-reported outcomes at 2- and 6-year follow-up intervals [12, 13]. This is a concern because the frequency and location of meniscus injury seen at the time of ACL reconstruction are associated with the patient sex, age, and surgical delay [35]. Slauterbeck et al. reported that at the time of ACL reconstruction, females are less likely to have a meniscus injury (56% compared with 71% for males), while males are more likely to have combined medial and lateral meniscus injuries (20% compared with 11% for females) [35]. Subjects with a delay between injury and ACL reconstructive surgery <3 months are least likely to have medial meniscus injury in comparison to those with a delay >3 months, and for subjects that are >35 years of age at the time of ACL reconstruction, meniscus injuries are more frequent and are more likely to occur in the medial compartment of the knee [35].

Many mechanisms are hypothesized to be associated with the increased rates of PTOA experienced by subjects that suffer an ACL injury with concomitant meniscal injury. An ACL-injured knee that has altered meniscus function has different gait patterns, increased magnitude of shear and compressive contact stresses during weight-bearing activity, cartilage proteoglycan changes, and increased fatigue, which combine to lead to progressive destruction of the collagen network [7]. At 10–15 year follow-up, greater deficits in quadriceps muscle strength were found in those with combined ACL and meniscal injury and/or chondral lesion compared with those with isolated ACL injuries [60]. Inferior cartilage proteoglycan content indicated by lower T1Gd was found with concomitant meniscectomy in the chronic phase after ACL injury [7]. Because meniscus damage is associated with higher risk of PTOA, many researchers have suggested repairing or preserving the meniscus as much as possible could be beneficial to the long-term health of the knee [2, 14, 34, 36, 57, 59].

Overall, concomitant meniscal injury increases the risk of inferior cartilage health; however, there is conflicting evidence in outcomes between ACL injury with concomitant medial versus lateral meniscus damage. Studies have reported that ACL injury in combination with lateral meniscus injury is associated with worse outcomes [1, 13], while other reports have linked ACL injury in combination with medial meniscus injury to worse outcomes [12, 61]. In addition, Jones et al. reported that a lateral

meniscus tear and/or partial lateral meniscectomy were associated with better outcomes [12]. They hypothesized that this finding may be associated with the mechanism of injury, such that when the impact force is transmitted across the lateral compartment at the time of ACL causing lateral meniscus injury, the joint fares better than that if the force is transmitted elsewhere [12]. Jones et al. also reported that medial meniscus injury correlated with the medial compartment joint space narrowing 2–3 years after injury [12]. A systematic review of this area of inquiry reported a small increase in PTOA rates for ACL injury with concomitant medial meniscus injury, no increases for the same ligament trauma with concomitant lateral meniscus injury, but, overall, determined the current literature was based on a low level of evidence [61].

3.6 Effect of Surgical Versus Nonsurgical Treatment of ACL Injury on PTOA

Despite the availability of many different surgical treatment options for a disrupted ACL, a long-term protective effect of ACL reconstruction against the onset and progression of PTOA has not been established. Numerous studies have demonstrated that surgical reconstruction does not change the long-term outcomes, between 2 years and up to 20 years postoperatively, in PTOA symptoms, or function when compared to rehabilitation without reconstruction [1, 11, 18, 22, 56, 58, 62–64]. The knee anterior cruciate ligament, nonsurgical versus surgical treatment (KANON) randomized controlled trial demonstrated that the treatment of ACL injury with reconstruction compared to rehabilitation with optional delayed surgical reconstruction had no significant differences in patient-reported outcomes at 2 years and no significant differences in patient-reported outcomes and radiographic evidence of PTOA at 5-year follow-up [62, 63]. An important limitation of the KANON trial is the transfer bias at 5-year follow-up, where 51% of those in the rehabilitation with optional delayed surgery treatment arm of the study chose to undergo ACL reconstruction surgery as time post injury progressed [63]. This high transfer rate may have introduced bias into the study. However, the study by Frobell et al. [62, 63] is the only clinical trail the authors could identify that has the capacity to provide insight into the efficacy of surgical versus nonsurgical treatment of ACL injury. In contrast to the findings of numerous studies, one meta-analysis reported that ACL reconstruction had a lower RR of PTOA than nonoperative treatment at a mean follow-up of 10 years; however, they also found that ACL reconstruction had a higher proportion of moderate/severe PTOA than the nonoperative group [10]. One possible explanation the authors provided for this finding was the differences in patient expectations and activity modifications between the reconstruction versus nonsurgical treatment groups [10]. Also, this meta-analysis only included studies that used radiographic-based Kellgren and Lawrence classification of PTOA, potentially excluding the findings from studies that used more sensitive MRI-based PTOA classification systems [10].

Even though the choice to undergo ACL reconstruction or nonsurgical treatment does not appear to impact long-term outcomes, reconstruction versus rehabilitation with nonsurgical treatment appears to undergo different biomechanical and biological responses. Surgical reconstruction creates additional trauma to the joint with a prolonged elevation of the inflammatory response after the initial injury [1, 65]. For example, treatment of ACL injury with reconstruction results in higher cytokine levels compared with nonsurgical treatment with rehabilitation, with enduring elevations of synovial fluid IL-6 and TNF that activate MMPs and aggrecanases, increase proteolytic degradation, and decrease the synthesis of aggrecan and type II collagen [65]. In addition, structural changes associated with reconstruction have been noted, with increased radiographic changes in the patellofemoral joint and subchondral bone surface curvature [22, 66]. ACL reconstruction has also been associated with larger BMLs at 6 months compared with the treatment with rehabilitation alone; however, at 12 months, no differences in BMLs between surgical versus nonsurgical treatments were present [67].

Although ACL reconstruction has a significant impact on the knee, treatment with rehabilitation alone has an important impact that should be appreciated. ACL-deficient knees undergo biomechanical changes that have the potential to impact other knee structures including the menisci and cartilage. For example, the rate of meniscal injuries increases in ACL-deficient knees over time [1, 2, 11, 57, 68]. In addition, studies have examined how the biochemical environment of the knee changes following an ACL injury. Chinzei et al. reported that untreated ACL tears leave remnants of the torn ACL in the joint that may release mediators which affect cartilage metabolism, leading them to suggest that unreconstructed tears are not completely benign and may influence cartilage homeostasis [69].

3.7 Effect of Timing of ACL Reconstruction Surgery on PTOA

Risk for meniscal injury could be an indication for ACL reconstruction and the time frame for the surgery, because the longer the knee is ACL-deficient, the risk of developing meniscal injuries increases. Early reconstruction, <3–6 months after injury, appears to be associated with a decreased rate of meniscal injuries and meniscal surgeries including meniscectomies [1, 2, 11, 35]. These findings suggest that the timing of reconstruction is important. Barenius et al. reported that patients undergoing early reconstruction (<6 months after the ACL injury) had higher health-related quality of life at 8 years [11]. In addition, Slauterbeck et al. reported patients undergoing ACL reconstruction with a surgical delay of >1 year were more likely to have an articular cartilage lesion (60% compared with 47% with a delay <1 year), and a surgical delay of ACL reconstruction >1 year resulted in a greater proportion of large and grade 3 lesions of the lateral femoral condyle [35]. However, early ACL reconstruction also produced higher inflammatory cytokines for a longer period than rehabilitation plus optional delayed reconstruction, suggesting that delaying reconstruction could have beneficial effects on the temporal inflammatory process of the injured knee [65]. Another study reported a shorter surgical delay was correlated with a slower cartilage recovery after running, which may be an important factor to consider in high-demand athletes [70]. In contrast, other studies present evidence that early versus delayed reconstruction does not have a significant effect on patient outcomes. Studies have not found a difference between partial or full meniscectomy and meniscal repair surgery rates from 5 to 20 years between early reconstruction versus rehabilitation alone with optional delayed reconstruction [18, 63]. These findings challenge the premise that ACL-deficient knees are at increased risk for meniscal injuries. Hunter et al. found that time from injury to surgery had no effect on bone curvature change seen after reconstruction, an outcome thought to reflect bone remodeling and early onset of PTOA [66]. In addition, other evidence suggests the time between injury and reconstruction is not a risk factor for OA and does not influence its development [11, 61]. Frobell et al. suggest there is no difference in PTOA rates between early reconstruction compared to delayed reconstruction 5 years following an ACL tear; however, it is important to note this study was not designed to directly assess the timing of surgery [63]. Overall, the literature remains unclear on whether the timing of reconstruction surgery has an impact on the risk of developing PTOA.

3.8 Effect of ACL Graft Material on PTOA

The graft material used to reconstruct the ACL is an important concern that impacts knee health and long-term outcomes; however, the effect of the graft material used to reconstruct the ACL on the risk of developing PTOA is unclear. A series of studies have reported that ACL reconstruction with a bone–patellar tendon–bone (BPTB) autograft results in a higher prevalence of PTOA in comparison to reconstruction with hamstring tendon autografts over an average of 2–10 and 18–20 year follow-up intervals [71–73]. Keays et al. reported that BPTB grafts had higher rates of tibiofemoral

OA than hamstring tendon grafts; however, the authors did not indicate if autografts were used [36]. BPTB autografts are often associated with patellofemoral issues such as pain when walking on hard ground, kneeling, and numbness of skin, usually due to donor site morbidity [2, 11, 74]. Despite the high levels of OA with BPTB autografts, they have demonstrated satisfactory outcomes at long-term follow-up with improvement in function compared to preinjury levels [2, 72]. However, these studies investigating BPTB autografts versus hamstring tendon autografts were only able to establish associations and not cause-and-effect relationships. In contrast, a few studies with a higher level of evidence found no difference in outcomes between BPTB or hamstring grafts. Two randomized controlled trials found no differences in PTOA rates after 10–14 years between BPTB or hamstring tendon autografts [11, 75]. Similarly, a cohort study, while finding higher rates of PTOA in patients reconstructed with BPTB autografts compared with hamstring tendon autografts, found equivalent long-term clinical outcomes between the graft types 20 years postoperatively [73]. Likewise, a meta-analysis by Xie et al. reported a slight increase in OA rates for BPTB autografts compared with hamstring tendon autografts at a minimum of 5 years, although they cautioned the significance of this result due to the overall heterogeneity of findings and differences in classifications of PTOA used between the studies included in the analysis [74].

Another area of inquiry is whether the use of autografts versus allografts to reconstruct the ACL has an impact on knee health, as allografts would theoretically avoid problems with donor site morbidity. Jones et al. found the reconstruction of the ACL with allografts to be a risk factor for worse patient-reported outcomes 2–6 years postoperatively, and Amano et al. reported the use of allograft was associated with elevated T1ρ and T2 times, indicating worse cartilage health 3 years postoperatively [12, 15]. In contrast, one case–control study of BPTB grafts found no significant differences in PTOA between auto and allografts at 3–13 years follow-up in high-activity level patients; however, this study had a small sample size, it used a retrospective study design, and did provide an a priori power analysis [76]. Overall, there does not appear to be a consensus in the literature on the effect of the type of graft material on long-term development of PTOA.

3.9 Effect of ACL Trauma on Patellofemoral and Tibiofemoral PTOA

Following ACL trauma, it is unclear if the pathoetiology of the PTOA disease process is different between the tibiofemoral and patellofemoral joints. For example, 5 years following an index ACL injury, Frobell et al. revealed that 12% of ACL-injured knees had tibiofemoral OA and 20% had patellofemoral OA, irrespective of the surgical or nonsurgical treatment of the torn ligament [63]. In addition, they observed that patellofemoral OA was more common with BPTB autografts than hamstring tendon autografts [63]. The authors hypothesized this may have been produced by the surgical trauma associated with harvesting the BPTB graft, altered biomechanics of the patellofemoral joint caused by postoperative change of the patella and patellar tendon geometry, bony remodeling response of the patella, or some combination of these mechanisms [63]. In contrast, Risberg et al. studied subjects that underwent ACL reconstruction with either BPTB or hamstring tendon autografts and revealed the prevalence of radiographic tibiofemoral and patellofemoral PTOA rates were 42% and 21%, correspondingly, 20 years postoperatively [34]. However, 25% and 14% had symptomatic tibiofemoral and patellofemoral PTOA, respectively [34]. Culvenor et al. conducted a systematic review and reported that the prevalence of PTOA was similar between patellofemoral and tibiofemoral joints at 0–5, 5–10, and 10–15 years following ACL reconstruction [77].

3.10 Return to Sport Considerations for Athletes

The heterogeneity of findings on the efficacy of having reconstruction with early or delayed surgery poses a challenge, especially for high-level

athletes. Overall, regardless of the treatment courses in athletes, ACL injury increases the risk of OA in the long term [18]. However, high-level athletes have significant demands placed on their knees that often differ remarkably from the general population. As such, the findings from studies whose subject population is not from elite athletics may not be generalizable to active individuals. The KANON trial by Frobell et al. demonstrated no difference in outcomes following ACL injury between treatment with reconstruction or rehabilitation alone and explicitly stated that their results do not apply to professional athletes [63]. Research that directly studies athletes may have more relevant findings. One study of 19 Olympic-level athletes from the 1960s with ACL injuries that did not undergo reconstruction reported that when these athletes returned to high-level activity, there was a 95% prevalence of meniscal and cartilage damage, osteoarthritis, instability, and severe symptoms after 20 years [78]. In addition, there was a 95% meniscectomy rate after 20 years and a 50% rate of total knee replacement after 35 years [78]. In elite soccer and alpine skiing athletes returning to their pre-injury sport, Hoffelner et al. found reconstruction did not increase the risk of PTOA, leading them to recommend that athletes returning to high-level sport undergo reconstruction [79]. Another study of high-level athletes found the treatment course did not affect PTOA rates, meniscectomy rates, and functional outcomes after 20 years and that the rates of PTOA in operatively treated athletes were 80% at 20 years [18]; however, these authors did report the reconstruction group had better knee stability [18].

To minimize risk from reconstruction due to the significant amount of acute changes it causes, it may be advisable to have extended recovery time after reconstruction and not rush back into sport [6, 67]. Van Ginckel et al. found cartilage showed decreased resiliency 6 months after surgery, with slower recovery of cartilage morphological characteristics after a running test [70]. This delayed cartilage recovery might cause maintained deformation and increased permeability of the articular cartilage [70]. As a result, the high-impact loading associated with participation in sports may lead to degeneration in these delayed recovery states [70]. These findings led Van Ginckel et al. to recommend that it may be important to consider a delayed RTS while cartilage is more fragile in the early phases after injury [70]. Culvenor et al. studied the impact of accelerated RTS after ACL reconstruction and found significantly greater odds of BMLs in those who returned to sport <10 months after reconstruction compared with those who did not return before 10 months [80]. These authors were unable to determine if these BMLs were new or persisted from the injury/surgery, but they theorized this may be a potential marker of early PTOA and an important factor to consider in RTS decisions [80].

It is important to note that athletes can RTS without the fear of guaranteeing worse outcomes in the long term. Oiestad et al. found patients who returned to planting, cutting, and pivoting sports had lower risk of symptomatic and radiographic PTOA at 15 years than those who did not return [81]. Keays et al. also found returning to sport did not increase the risk of PTOA [36]. These studies [36, 81] were not designed to establish the cause-and-effect relationships and can only show associations. Even though it is unclear whether RTS is due to confounding factors such as higher baseline knee function, results suggest for those with adequate knee function in the early phase, return to pivoting sport may not harm long-term knee health [81].

3.11 Limitations of the Current Literature

The complexity and insidious nature of PTOA has posed serious challenges for research. Very few RCTs have been designed to establish the mechanistic cause-and-effect relationship between severe knee trauma that involves disruption of the ACL to the onset and progression of PTOA. As such, very few conclusions on the cause-and-effect relationships can be made. There are many classification systems for PTOA, making it hard to compare the findings of studies that used different classifications. Also, because of the long-term nature associ-

ated with the development of PTOA, studies often take years if not decades to complete. As a result, the surgical and rehabilitation techniques used in studies may often become outdated, limiting the generalizability of the findings to current clinical practice. In addition, many studies have had heterogeneous results and relatively small sample sizes, making it hard to make overall inferences and limiting their applicability. Studies usually have an over-representation of males [10], and findings from these samples may not be suitable to the disease processes that occur in females. Similarly, samples often do not adequately represent elite athlete populations. Because athletes have significant differences in strengths and demands placed on their lower extremities compared with the general population, findings from studies that focus on the general population may not apply to elite athletes. More research is needed to assess the unique factors that affect the PTOA process in athletes.

References

1. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. Am J Sports Med. 2007;35(10):1756–69. https://doi.org/10.1177/0363546507307396.
2. Ahn JH, Kim JG, Wang JH, Jung CH, Lim HC. Long-term results of anterior cruciate ligament reconstruction using bone-patellar tendon-bone: an analysis of the factors affecting the development of osteoarthritis. Arthroscopy. 2012;28(8):1114–23. https://doi.org/10.1016/j.arthro.2011.12.019.
3. Pedoia V, Su F, Amano K, Li Q, McCulloch CE, Souza RB, et al. Analysis of the articular cartilage T1rho and T2 relaxation times changes after ACL reconstruction in injured and contralateral knees and relationships with bone shape. J Orthop Res. 2017;35(3):707–17. https://doi.org/10.1002/jor.23398.
4. Williams A, Winalski CS, Chu CR. Early articular cartilage MRI T2 changes after anterior cruciate ligament reconstruction correlate with later changes in T2 and cartilage thickness. J Orthop Res. 2017;35(3):699–706. https://doi.org/10.1002/jor.23358.
5. Chen E, Amano K, Pedoia V, Souza RB, Ma CB, Li X. Longitudinal analysis of tibiofemoral cartilage contact area and position in ACL reconstructed patients. J Orthop Res. 2018;36(10):2718–27. https://doi.org/10.1002/jor.24024.
6. Van Ginckel A, Verdonk P, Witvrouw E. Cartilage adaptation after anterior cruciate ligament injury and reconstruction: implications for clinical management and research? A systematic review of longitudinal MRI studies. Osteoarthr Cartil. 2013;21(8):1009–24. https://doi.org/10.1016/j.joca.2013.04.015.
7. Neuman P, Tjornstrand J, Svensson J, Ragnarsson C, Roos H, Englund M, et al. Longitudinal assessment of femoral knee cartilage quality using contrast enhanced MRI (dGEMRIC) in patients with anterior cruciate ligament injury--comparison with asymptomatic volunteers. Osteoarthr Cartil. 2011;19(8):977–83. https://doi.org/10.1016/j.joca.2011.05.002.
8. Lonza GC, Gardner-Morse MG, Vacek PM, Beynnon BD. Radiographic-based measurement of tibiofemoral joint space width and magnetic resonance imaging derived articular cartilage thickness are not related in subjects at risk for post traumatic arthritis of the knee. J Orthop Res. 2019;37(5):1052–8. https://doi.org/10.1002/jor.24283.
9. Anderson DD, Chubinskaya S, Guilak F, Martin JA, Oegema TR, Olson SA, et al. Post-traumatic osteoarthritis: improved understanding and opportunities for early intervention. J Orthop Res. 2011;29(6):802–9. https://doi.org/10.1002/jor.21359.
10. Ajuied A, Wong F, Smith C, Norris M, Earnshaw P, Back D, et al. Anterior cruciate ligament injury and radiologic progression of knee osteoarthritis: a systematic review and meta-analysis. Am J Sports Med. 2014;42(9):2242–52. https://doi.org/10.1177/0363546513508376.
11. Barenius B, Ponzer S, Shalabi A, Bujak R, Norlen L, Eriksson K. Increased risk of osteoarthritis after anterior cruciate ligament reconstruction: a 14-year follow-up study of a randomized controlled trial. Am J Sports Med. 2014;42(5):1049–57. https://doi.org/10.1177/0363546514526139.
12. Jones MH, Spindler KP. Risk factors for radiographic joint space narrowing and patient reported outcomes of post-traumatic osteoarthritis after ACL reconstruction: data from the MOON cohort. J Orthop Res. 2017;35(7):1366–74. https://doi.org/10.1002/jor.23557.
13. Spindler KP, Huston LJ, Chagin KM, Kattan MW, Reinke EK, Amendola A, et al. Ten-year outcomes and risk factors after anterior cruciate ligament reconstruction: a MOON longitudinal prospective cohort study. Am J Sports Med. 2018;46(4):815–25. https://doi.org/10.1177/0363546517749850.
14. Li RT, Lorenz S, Xu Y, Harner CD, Fu FH, Irrgang JJ. Predictors of radiographic knee osteoarthritis after anterior cruciate ligament reconstruction. Am J Sports Med. 2011;39(12):2595–603. https://doi.org/10.1177/0363546511424720.
15. Amano K, Huebner JL, Stabler TV, Tanaka M, McCulloch CE, Lobach I, et al. Synovial fluid profile at the time of anterior cruciate ligament reconstruction and its association with cartilage matrix composition 3 years after surgery. Am J Sports Med. 2018;46(4):890–9. https://doi.org/10.1177/0363546517749834.

16. Doherty M, Watt I, Dieppe P. Influence of primary generalised osteoarthritis on development of secondary osteoarthritis. Lancet. 1983;2(8340):8–11.
17. Englund M, Paradowski PT, Lohmander LS. Association of radiographic hand osteoarthritis with radiographic knee osteoarthritis after meniscectomy. Arthritis Rheum. 2004;50(2):469–75. https://doi.org/10.1002/art.20035.
18. van Yperen DT, Reijman M, van Es EM, Bierma-Zeinstra SMA, Meuffels DE. Twenty-year follow-up study comparing operative versus nonoperative treatment of anterior cruciate ligament ruptures in high-level athletes. Am J Sports Med. 2018;46(5):1129–36. https://doi.org/10.1177/0363546517751683.
19. Madaleno FO, Santos BA, Araujo VL, Oliveira VC, Resende RA. Prevalence of knee osteoarthritis in former athletes: a systematic review with meta-analysis. Braz J Phys Ther. 2018;22:437–51. https://doi.org/10.1016/j.bjpt.2018.03.012.
20. Driban JB, Hootman JM, Sitler MR, Harris KP, Cattano NM. Is participation in certain sports associated with knee osteoarthritis? A systematic review. J Athl Train. 2017;52(6):497–506. https://doi.org/10.4085/1062-6050-50.2.08.
21. Smith MV, Nepple JJ, Wright RW, Matava MJ, Brophy RH. Knee osteoarthritis is associated with previous meniscus and anterior cruciate ligament surgery among Elite College American football athletes. Sports Health. 2017;9(3):247–51. https://doi.org/10.1177/1941738116683146.
22. Lohmander LS, Ostenberg A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthritis Rheum. 2004;50(10):3145–52. https://doi.org/10.1002/art.20589.
23. von Porat A, Roos EM, Roos H. High prevalence of osteoarthritis 14 years after an anterior cruciate ligament tear in male soccer players: a study of radiographic and patient relevant outcomes. Ann Rheum Dis. 2004;63(3):269–73.
24. Simon JE, Grooms DR, Docherty CL. The long term impact of osteoarthritis following knee surgery in former collegiate athletes. J Sport Rehabil. 2017:1–19. https://doi.org/10.1123/jsr.2017-0115.
25. Losina E, Weinstein AM, Reichmann WM, Burbine SA, Solomon DH, Daigle ME, et al. Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. Arthritis Care Res. 2013;65(5):703–11. https://doi.org/10.1002/acr.21898.
26. Beynnon BD, Johnson RJ, Abate JA, Fleming BC, Nichols CE. Treatment of anterior cruciate ligament injuries, part I. Am J Sports Med. 2005;33(10):1579–602. https://doi.org/10.1177/0363546505279913.
27. Beynnon BD, Johnson RJ, Abate JA, Fleming BC, Nichols CE. Treatment of anterior cruciate ligament injuries, part 2. Am J Sports Med. 2005;33(11):1751–67. https://doi.org/10.1177/0363546505279922.
28. Bowers AL, Spindler KP, McCarty EC, Arrigain S. Height, weight, and BMI predict intra-articular injuries observed during ACL reconstruction: evaluation of 456 cases from a prospective ACL database. Clin J Sport Med. 2005;15(1):9–13.
29. Noyes FR, Bassett RW, Grood ES, Butler DL. Arthroscopy in acute traumatic hemarthrosis of the knee. Incidence of anterior cruciate tears and other injuries. J Bone Joint Surg. 1980;62(5):687–95, 757.
30. Piasecki DP, Spindler KP, Warren TA, Andrish JT, Parker RD. Intraarticular injuries associated with anterior cruciate ligament tear: findings at ligament reconstruction in high school and recreational athletes. An analysis of sex-based differences. Am J Sports Med. 2003;31(4):601–5. https://doi.org/10.1177/03635465030310042101.
31. Speer KP, Spritzer CE, Goldner JL, Garrett WE Jr. Magnetic resonance imaging of traumatic knee articular cartilage injuries. Am J Sports Med. 1991;19(4):396–402. https://doi.org/10.1177/036354659101900414.
32. Vellet AD, Marks PH, Fowler PJ, Munro TG. Occult posttraumatic osteochondral lesions of the knee: prevalence, classification, and short-term sequelae evaluated with MR imaging. Radiology. 1991;178(1):271–6. https://doi.org/10.1148/radiology.178.1.1984319.
33. Spindler KP, Wright RW. Clinical practice. Anterior cruciate ligament tear. N Engl J Med. 2008;359(20):2135–42. https://doi.org/10.1056/NEJMcp0804745.
34. Risberg MA, Oiestad BE, Gunderson R, Aune AK, Engebretsen L, Culvenor A, et al. Changes in knee osteoarthritis, symptoms, and function after anterior cruciate ligament reconstruction: a 20-year prospective follow-up study. Am J Sports Med. 2016;44(5):1215–24. https://doi.org/10.1177/0363546515626539.
35. Slauterbeck JR, Kousa P, Clifton BC, Naud S, Tourville TW, Johnson RJ, et al. Geographic mapping of meniscus and cartilage lesions associated with anterior cruciate ligament injuries. J Bone Joint Surg. 2009;91(9):2094–103. https://doi.org/10.2106/jbjs.H.00888.
36. Keays SL, Newcombe PA, Bullock-Saxton JE, Bullock MI, Keays AC. Factors involved in the development of osteoarthritis after anterior cruciate ligament surgery. Am J Sports Med. 2010;38(3):455–63. https://doi.org/10.1177/0363546509350914.
37. Argentieri EC, Sturnick DR, DeSarno MJ, Gardner-Morse MG, Slauterbeck JR, Johnson RJ, et al. Changes to the articular cartilage thickness profile of the tibia following anterior cruciate ligament injury. Osteoarthr Cartil. 2014;22(10):1453–60. https://doi.org/10.1016/j.joca.2014.06.025.
38. Owusu-Akyaw KA, Kim SY, Spritzer CE, Collins AT, Englander ZA, Utturkar GM, et al. Determination of the position of the knee at the time of an anterior cruciate ligament rupture for male versus female patients by an analysis of bone bruises. Am J Sports Med. 2018;46(7):1559–65. https://doi.org/10.1177/0363546518764681.
39. Lynch TC, Crues JV 3rd, Morgan FW, Sheehan WE, Harter LP, Ryu R. Bone abnormalities of the knee: prevalence and significance at MR imag-

ing. Radiology. 1989;171(3):761–6. https://doi.org/10.1148/radiology.171.3.2717748.
40. Newberg AH, Wetzner SM. Bone bruises: their patterns and significance. Semin Ultrasound CT MR. 1994;15(5):396–409.
41. Eustace S, Keogh C, Blake M, Ward RJ, Oder PD, Dimasi M. MR imaging of bone oedema: mechanisms and interpretation. Clin Radiol. 2001;56(1):4–12. https://doi.org/10.1053/crad.2000.0585.
42. Sievanen H, Kannus P, Heinonen A, Oja P, Vuori I. Bone mineral density and muscle strength of lower extremities after long-term strength training, subsequent knee ligament injury and rehabilitation: a unique 2-year follow-up of a 26-year-old female student. Bone. 1994;15(1):85–90.
43. Kannus P, Sievanen H, Jarvinen M, Heinonen A, Oja P, Vuori I. A cruciate ligament injury produces considerable, permanent osteoporosis in the affected knee. J Bone Miner Res. 1992;7(12):1429–34. https://doi.org/10.1002/jbmr.5650071210.
44. van Meer BL, Oei EH, Bierma-Zeinstra SM, van Arkel ER, Verhaar JA, Reijman M, et al. Are magnetic resonance imaging recovery and laxity improvement possible after anterior cruciate ligament rupture in nonoperative treatment? Arthroscopy. 2014;30(9):1092–9. https://doi.org/10.1016/j.arthro.2014.04.098.
45. Bayar A, Sarikaya S, Keser S, Ozdolap S, Tuncay I, Ege A. Regional bone density changes in anterior cruciate ligament deficient knees: a DEXA study. Knee. 2008;15(5):373–7. https://doi.org/10.1016/j.knee.2008.05.005.
46. Nyland J, Fisher B, Brand E, Krupp R, Caborn DN. Osseous deficits after anterior cruciate ligament injury and reconstruction: a systematic literature review with suggestions to improve osseous homeostasis. Arthroscopy. 2010;26(9):1248–57. https://doi.org/10.1016/j.arthro.2010.03.017.
47. Frobell RB, Roos HP, Roos EM, Hellio Le Graverand MP, Buck R, Tamez-Pena J, et al. The acutely ACL injured knee assessed by MRI: are large volume traumatic bone marrow lesions a sign of severe compression injury? Osteoarthr Cartil. 2008;16(7):829–36. https://doi.org/10.1016/j.joca.2007.11.003.
48. Papalia R, Torre G, Vasta S, Zampogna B, Pedersen DR, Denaro V, et al. Bone bruises in anterior cruciate ligament injured knee and long-term outcomes. A review of the evidence. Open Access J Sports Med. 2015;6:37–48. https://doi.org/10.2147/oajsm.S75345.
49. Li H, Chen C, Chen S. Posttraumatic knee osteoarthritis following anterior cruciate ligament injury: potential biochemical mediators of degenerative alteration and specific biochemical markers. Biomed Rep. 2015;3(2):147–51. https://doi.org/10.3892/br.2014.404.
50. Struglics A, Okroj M, Sward P, Frobell R, Saxne T, Lohmander LS, et al. The complement system is activated in synovial fluid from subjects with knee injury and from patients with osteoarthritis. Arthritis Res Ther. 2016;18(1):223. https://doi.org/10.1186/s13075-016-1123-x.
51. Coughlin TR, Kennedy OD. The role of subchondral bone damage in post-traumatic osteoarthritis. Ann N Y Acad Sci. 2016;1383(1):58–66. https://doi.org/10.1111/nyas.13261.
52. Koster IM, Oei EH, Hensen JH, Boks SS, Koes BW, Vroegindeweij D, et al. Predictive factors for new onset or progression of knee osteoarthritis one year after trauma: MRI follow-up in general practice. Eur Radiol. 2011;21(7):1509–16. https://doi.org/10.1007/s00330-011-2089-3.
53. Theologis AA, Kuo D, Cheng J, Bolbos RI, Carballido-Gamio J, Ma CB, et al. Evaluation of bone bruises and associated cartilage in anterior cruciate ligament-injured and -reconstructed knees using quantitative t(1rho) magnetic resonance imaging: 1-year cohort study. Arthroscopy. 2011;27(1):65–76. https://doi.org/10.1016/j.arthro.2010.06.026.
54. Gong J, Pedoia V, Facchetti L, Link TM, Ma CB, Li X. Bone marrow edema-like lesions (BMELs) are associated with higher T1rho and T2 values of cartilage in anterior cruciate ligament (ACL)-reconstructed knees: a longitudinal study. Quant Imaging Med Surg. 2016;6(6):661–70. https://doi.org/10.21037/qims.2016.12.11.
55. Frobell RB. Change in cartilage thickness, posttraumatic bone marrow lesions, and joint fluid volumes after acute ACL disruption: a two-year prospective MRI study of sixty-one subjects. J Bone Joint Surg. 2011;93(12):1096–103. https://doi.org/10.2106/jbjs.J.00929.
56. Nordenvall R, Bahmanyar S, Adami J, Mattila VM, Fellander-Tsai L. Cruciate ligament reconstruction and risk of knee osteoarthritis: the association between cruciate ligament injury and post-traumatic osteoarthritis. a population based nationwide study in Sweden, 1987-2009. PLoS One. 2014;9(8):e104681. https://doi.org/10.1371/journal.pone.0104681.
57. Magnussen RA, Duthon V, Servien E, Neyret P. Anterior cruciate ligament reconstruction and osteoarthritis: evidence from long-term follow-up and potential solutions. Cartilage. 2013;4(3 Suppl):22s–6s. https://doi.org/10.1177/1947603513486559.
58. Oiestad BE, Engebretsen L, Storheim K, Risberg MA. Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. Am J Sports Med. 2009;37(7):1434–43. https://doi.org/10.1177/0363546509338827.
59. Claes S, Hermie L, Verdonk R, Bellemans J, Verdonk P. Is osteoarthritis an inevitable consequence of anterior cruciate ligament reconstruction? A meta-analysis. Knee Surg Sports Traumatol Arthrosc. 2013;21(9):1967–76. https://doi.org/10.1007/s00167-012-2251-8.

60. Oiestad BE, Holm I, Aune AK, Gunderson R, Myklebust G, Engebretsen L, et al. Knee function and prevalence of knee osteoarthritis after anterior cruciate ligament reconstruction: a prospective study with 10 to 15 years of follow-up. Am J Sports Med. 2010;38(11):2201–10. https://doi.org/10.1177/0363546510373876.
61. van Meer BL, Meuffels DE, van Eijsden WA, Verhaar JA, Bierma-Zeinstra SM, Reijman M. Which determinants predict tibiofemoral and patellofemoral osteoarthritis after anterior cruciate ligament injury? A systematic review. Br J Sports Med. 2015;49(15):975–83. https://doi.org/10.1136/bjsports-2013-093258.
62. Frobell RB, Roos EM, Roos HP, Ranstam J, Lohmander LS. A randomized trial of treatment for acute anterior cruciate ligament tears. N Engl J Med. 2010;363(4):331–42. https://doi.org/10.1056/NEJMoa0907797.
63. Frobell RB, Roos HP, Roos EM, Roemer FW, Ranstam J, Lohmander LS. Treatment for acute anterior cruciate ligament tear: five year outcome of randomised trial. BMJ. 2013;346:f232. https://doi.org/10.1136/bmj.f232.
64. Meuffels DE, Favejee MM, Vissers MM, Heijboer MP, Reijman M, Verhaar JA. Ten year follow-up study comparing conservative versus operative treatment of anterior cruciate ligament ruptures. A matched-pair analysis of high level athletes. Br J Sports Med. 2009;43(5):347–51. https://doi.org/10.1136/bjsm.2008.049403.
65. Larsson S, Struglics A, Lohmander LS, Frobell R. Surgical reconstruction of ruptured anterior cruciate ligament prolongs trauma-induced increase of inflammatory cytokines in synovial fluid: an exploratory analysis in the KANON trial. Osteoarthr Cartil. 2017;25(9):1443–51. https://doi.org/10.1016/j.joca.2017.05.009.
66. Hunter DJ, Lohmander LS, Makovey J, Tamez-Pena J, Totterman S, Schreyer E, et al. The effect of anterior cruciate ligament injury on bone curvature: exploratory analysis in the KANON trial. Osteoarthr Cartil. 2014;22(7):959–68. https://doi.org/10.1016/j.joca.2014.05.014.
67. Frobell RB, Le Graverand MP, Buck R, Roos EM, Roos HP, Tamez-Pena J, et al. The acutely ACL injured knee assessed by MRI: changes in joint fluid, bone marrow lesions, and cartilage during the first year. Osteoarthr Cartil. 2009;17(2):161–7. https://doi.org/10.1016/j.joca.2008.06.020.
68. Fithian DC, Paxton EW, Stone ML, Luetzow WF, Csintalan RP, Phelan D, et al. Prospective trial of a treatment algorithm for the management of the anterior cruciate ligament-injured knee. Am J Sports Med. 2005;33(3):335–46. https://doi.org/10.1177/0363546504269590.
69. Chinzei N, Brophy RH, Duan X, Cai L, Nunley RM, Sandell LJ, et al. Molecular influence of anterior cruciate ligament tear remnants on chondrocytes: a biologic connection between injury and osteoarthritis. Osteoarthr Cartil. 2018;26(4):588–99. https://doi.org/10.1016/j.joca.2018.01.017.
70. Van Ginckel A, Verdonk P, Victor J, Witvrouw E. Cartilage status in relation to return to sports after anterior cruciate ligament reconstruction. Am J Sports Med. 2013;41(3):550–9. https://doi.org/10.1177/0363546512473568.
71. Mascarenhas R, Tranovich MJ, Kropf EJ, Fu FH, Harner CD. Bone-patellar tendon-bone autograft versus hamstring autograft anterior cruciate ligament reconstruction in the young athlete: a retrospective matched analysis with 2-10 year follow-up. Knee Surg Sports Traumatol Arthrosc. 2012;20(8):1520–7. https://doi.org/10.1007/s00167-011-1735-2.
72. Ettinger M, Etter F, Calliess T, Bohnsack M, Becher C. Long term results of bone-patella-tendon-bone ACL reconstruction. J Orthop. 2017;14(1):91–4. https://doi.org/10.1016/j.jor.2016.10.027.
73. Thompson SM, Salmon LJ, Waller A, Linklater J, Roe JP, Pinczewski LA. Twenty-year outcome of a longitudinal prospective evaluation of isolated endoscopic anterior cruciate ligament reconstruction with patellar tendon or hamstring autograft. Am J Sports Med. 2016;44(12):3083–94. https://doi.org/10.1177/0363546516658041.
74. Xie X, Xiao Z, Li Q, Zhu B, Chen J, Chen H, et al. Increased incidence of osteoarthritis of knee joint after ACL reconstruction with bone-patellar tendon-bone autografts than hamstring autografts: a meta-analysis of 1,443 patients at a minimum of 5 years. Eur J Orthop Surg Traumatol. 2015;25(1):149–59. https://doi.org/10.1007/s00590-014-1459-3.
75. Holm I, Oiestad BE, Risberg MA, Aune AK. No difference in knee function or prevalence of osteoarthritis after reconstruction of the anterior cruciate ligament with 4-strand hamstring autograft versus patellar tendon-bone autograft: a randomized study with 10-year follow-up. Am J Sports Med. 2010;38(3):448–54. https://doi.org/10.1177/0363546509350301.
76. Mascarenhas R, Tranovich M, Karpie JC, Irrgang JJ, Fu FH, Harner CD. Patellar tendon anterior cruciate ligament reconstruction in the high-demand patient: evaluation of autograft versus allograft reconstruction. Arthroscopy. 2010;26(9 Suppl):S58–66. https://doi.org/10.1016/j.arthro.2010.01.004.
77. Culvenor AG, Cook JL, Collins NJ, Crossley KM. Is patellofemoral joint osteoarthritis an under-recognised outcome of anterior cruciate ligament reconstruction? A narrative literature review. Br J Sports Med. 2013;47(2):66–70. https://doi.org/10.1136/bjsports-2012-091490.
78. Nebelung W, Wuschech H. Thirty-five years of follow-up of anterior cruciate ligament-deficient knees in high-level athletes. Arthroscopy. 2005;21(6):696–702. https://doi.org/10.1016/j.arthro.2005.03.010.

79. Hoffelner T, Resch H, Moroder P, Atzwanger J, Wiplinger M, Hitzl W, et al. No increased occurrence of osteoarthritis after anterior cruciate ligament reconstruction after isolated anterior cruciate ligament injury in athletes. Arthroscopy. 2012;28(4):517–25. https://doi.org/10.1016/j.arthro.2011.09.014.
80. Culvenor AG, Patterson BE, Guermazi A, Morris HG, Whitehead TS, Crossley KM. Accelerated return to sport after anterior cruciate ligament reconstruction and early knee osteoarthritis features at 1 year: an exploratory study. PM R. 2018;10(4):349–56. https://doi.org/10.1016/j.pmrj.2017.09.005.
81. Oiestad BE, Holm I, Risberg MA. Return to pivoting sport after ACL reconstruction: association with osteoarthritis and knee function at the 15-year follow-up. Br J Sports Med. 2018;52(18):1199–204. https://doi.org/10.1136/bjsports-2017-097718.