Articular Cartilage Repair of the Knee in Children and Adolescents

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Articular cartilage predominantly serves a biomechanical function, which begins in utero and further develops during growth and locomotion. With regard to its 2-tissue structure (chondrocytes and matrix), the regenerative potential of hyaline cartilage defects is limited. Children and adolescents are increasingly suffering from articular cartilage and osteochondral deficiencies. Traumatic incidents often result in damage to the joint surfaces, while repetitive microtrauma may cause osteochondritis dissecans. When compared with their adult counterparts, children and adolescents have a greater capacity to regenerate articular cartilage defects. Even so, articular cartilage injuries in this age group may predispose them to premature osteoarthritis. Consequently, surgery is indicated in young patients when conservative measures fail. The operative techniques for articular cartilage injuries traditionally performed in adults may be performed in children, although an individualized approach must be tailored according to patient and defect characteristics. Clear guidelines for defect dimension–associated techniques have not been reported. Knee joint dimensions must be considered and correlated with respect to the cartilage defect size. Particular attention must be given to the subchondral bone, which is frequently affected in children and adolescents. Articular cartilage repair techniques appear to be safe in this cohort of patients, and no differences in complication rates have been reported when compared with adult patients. Particularly, autologous chondrocyte implantation has good biological potential, especially for large-diameter joint surface defects.

Keywords: cartilage; knee; children; adolescents; osteochondritis dissecans; joint

The ability of body tissues and organs to regenerate after an injury depends on their level of specialization. Articular cartilage is highly specialized tissue. In turn, it does not possess highly effective repair mechanisms. Articular cartilage defects consequently constitute a difficult medical problem. Traumatic incidents are the leading cause of injuries to the articulating surfaces of large joints, that is, the knee joint, among children and adolescents. The increase in sports participation has resulted in more articular cartilage injuries[21] in younger patients. Articular cartilage defects in the knee[85] with the potential to develop into osteoarthritis (OA) pose a significant medical and socioeconomic dilemma.[38] In general, surgery is indicated for symptomatic chondral and osteochondral lesions to improve symptoms and prevent OA. Different surgical techniques as well as guidelines on how to treat the respective lesions are available to the surgeon.[48] Even though treatment in pediatric patients is comparable with adults, there are certain differences that result in alternative treatment algorithms. The aim of this narrative review was to describe the differences in the articular cartilage of children and adults; typical chondral, osteochondral, and osteochondritis dissecans (OD) lesions; surgical treatment modalities; and outcomes among children and adolescents.

CHILDREN AND ADOLESCENTS

Biologically, a child is a human between the stages of birth and puberty. Adolescence is a transitional stage of physical and psychological human development that generally occurs during the period from puberty to legal adulthood. Respecting the fact that children and adolescents are physiologically growing, their regeneration potential is greater than their adult counterparts, particularly when compared with older adults. Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability. This deterioration is the primary risk factor for major human diseases, including OA.

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The authors declared that they have no conflicts of interest in the authorship and publication of this contribution.

The Orthopaedic Journal of Sports Medicine, 6(3), 2325967118760190
DOI: 10.1177/2325967118760190

The rate of aging is controlled, at least to some extent, by genetic pathways and biochemical processes conserved in evolution. There are tentative hallmarks that represent common denominators of aging in different organisms, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. The resulting tissue/cellular differentiation and proliferation potential in young patients are more potent than those in adult patients.

Tissue regeneration is a property generally attributed to nonmammalian organisms. For example, *Hydra* and *Planaria* can regenerate their entire bodies from a small fraction of their tissue. Similarly, vertebrates, including newts and salamanders, can regenerate limbs or other structures after amputation. In contrast, the regenerative capacity in mammals is extremely limited and is generally confined to shedding and regrowth of antlers in deer and moose and ear-wound closure in rabbits. Despite this limited regeneration in adult mammals, supporting evidence suggests that certain mouse strains possess unusual abilities to regenerate/repair tissues in adulthood, including hyaline cartilage. Rai and Sandell[65] found significant variation in ear-wound healing capacity between different strains of mice. Mice with good ear-healing capacity also showed significantly better cartilage regeneration. However, there are no reports on an improved articular cartilage defect healing potential among children/adolescents compared with adults. Nevertheless, Pestka and colleagues[63] detected differences in in vitro analyses of cartilage tissue samples designated for secondary autologous chondrocyte implantation (ACI). The expression rates of the chondrocyte surface marker CD44, collagen type II, and aggrecan were significantly higher in patients under 20 years of age than in patients between the age of 20 and 50 years. The study suggests that chondrocytes from younger patients possess a reparative/chondrogenic potential that could lead to improved cartilage healing.

Clinically after ACI, Niemeyer et al[54] reported that postoperative International Knee Documentation Committee (IKDC) scores at 6, 12, and 24 months were significantly influenced by collagen type II expression, CD44 expression, and cell viability (higher expression, better outcome). The authors concluded that cell quality influences clinical outcomes after ACI in patients with a cartilage defect in the knee joint.[54] In line with these results, Fehrer and Lepperdinger[22] summarized that aged human mesenchymal stem cells (MSCs) show a decline in the differentiation potential as well as in the proliferation rate. The latter most likely reflects the fact that aged MSCs suffer from eroded telomeres. Furthermore, the fitness of the MSC population is significantly influenced by their pericellular environment as well as by the good health of the organ in which they reside.[22]

Children and adolescents are equipped with an increased regeneration potential, which includes the chondrocyte and stem cell populations. Such an increased cellular proliferation capacity and plasticity is directly linked to highly effective self-renewal processes even within tissue that has limited repair capacity in adults.

ARTICULAR CARTILAGE ANATOMY

The development of mesenchyme into connective tissue such as articular cartilage is not entirely predetermined by genetics but is also dependent on biomechanical input. The maintenance of cartilage and bone requires continued biomechanical input. Chondrocytes arise from mesenchyme or from mitosis of mature cells in situ. Mesenchymal cells aggregate to form a blastema around 5 weeks of gestation. These cells begin to secrete an extracellular matrix and are then called chondroblasts. As development progresses, the developing cartilage matrix gradually pushes the cells apart. The mesenchymal tissue surrounding the blastema gives rise to a membrane called the perichondrium. As children grow, their joints grow with them, and this growth involves progressive, circumferential expansion of the cartilaginous surface concurrent with expansion and thickening of the underlying bony epiphysis. Long bone lengthening predominantly takes place at the epiphyseal growth plates. The overlying epiphysis also grows, and its cartilaginous cap serves as a secondary growth plate.

Current evidence suggests that MSCs are abundant at the junction of the periosteum and synovium. From there, the MSCs migrate to the cartilage surface, migrate toward the physis, and differentiate into chondrocytes, depositing the extracellular matrix in the process. MSCs also support the continuous renewal and repair of tissues, including articular cartilage.[37] It has been described that a certain population of MSCs resides within superficial cartilage layers and may contribute to cartilage defect repair.[6] For the process of growth, MSCs migrate to the physis for hypertrophic (endochondral) ossification.[60]

Jones and coworkers[30] reported that articular cartilage volume in children may be very responsive to environmental manipulation . Children who participated in more vigorous sports gained twice as much articular cartilage than did less active children (identified by the frequency of vigorous exercise or watching more than 3 h/d of television or video games). Finally, chondrocyte movement has been described by Morales[47] as another prerequisite for articular cartilage development. With maturity, the subsurface proliferation of chondrocytes stops, and normal adult human cartilage appears to become postmitotic. Yet, the energetic function is comparable with many other cells across the body when adenosine triphosphate turnover is regarded. The bradytroph character of hyaline cartilage is interrelated with the low number of chondrocytes per volume. Once ossification ceases at the secondary growth center, osteochondral permeability diminishes markedly, a layer of calcified cartilage appears above the osteochondral junction, and the border between uncalcified and calcified cartilage is marked for the first time by a hematoxyphilic line known as the tidemark (see below).

The development of this tidemark represents one major difference between children/adolescents and skeletally mature adults. Direct blood flow into the overlying

TABLE 1
Articular Chondral and Osteochondral Lesions in the Knee Joint Among Children and Adolescents

Anatomic differences exist among adult and children/adolescent articular cartilage, which are mainly related to direct vascular access from the subchondral bone to the cartilage layer.
Prepubertal patients are equipped with a stronger cellular regeneration potential than adults; chondrocytes and stem cells have superior proliferation and differentiation properties.
Chondral and osteochondral lesions are highly frequent among children and adolescents, most often related to sports injuries.
The knee joint is the most often affected location.
Osteochondral abnormalities are more frequent than chondral abnormalities.
Traumatic patellar dislocations are the most frequent underlying abnormality resulting in joint surface abnormalities.
Osteochondritis dissecans is the most frequent nontraumatic abnormality resulting in articular cartilage defects.
Degenerative articular cartilage defects occur very seldom.

cartilage persists until the tidemark is cemented. Cartilage nutrition is then accomplished by way of diffusion from synovial fluid. Nutrition via diffusion is much less potent than through direct blood flow, thus leading to a reduced regenerative potential. As soon as the epiphyseal growth plates are closed, adolescents are considered skeletally mature and are "biologically young adults" regarding their skeletal system and joint cartilage. This transition occurs around the age of 14 years in boys and 13 years in girls. Complete closure of the epiphyseal growth plate in the femur and tibia is achieved at ages up to 21 years, so that skeletal maturity varies widely.

From an anatomic standpoint (Table 1), the transition to articular cartilage possessing less regenerative potential can be defined: appositional growth is completed with clearly diminished MSC quantity and activity as well as a change in nutrition from direct blood flow to diffusion via the joint cavity.

TRAUMATIC JOINT SURFACE ABNORMALITIES

Trauma is the main cause of cartilage defects in children and adolescents. The increased participation of children and adolescents in organized sports worldwide is a welcome trend, given the evidence of lower physical fitness and an increased prevalence of overweight in this population.[83] However, the increased sports activity of children starting at an early age and continuing through the years of growth raises concerns about the injury risk and severity. Anterior cruciate ligament (ACL) damage as well as physeal injuries are among the most frequent within this population.[5] Both are considered potentially serious with regard to OA initiation[76] and furthermore often simultaneously result in articular cartilage defects.[14,39] Isolated, and more often combined, chondral and osteochondral injuries of the knee are also becoming increasingly prevalent in the pediatric population.[58]

Trauma-related osteochondral fractures at other sites (other than the patella and lateral femoral condyle) across the adolescent knee joint are very rare. The exact incidence of symptomatic high-grade chondral injuries is poorly defined. It has been reported that between 5% and 10% of active patients younger than 40 years who present with hemarthrosis of the knee after a known traumatic event will have a focal chondral injury.[3,4] Typically, a direct blow to the knee, extreme shearing forces, or luxation events result in an articular cartilage injury.[34] Using magnetic resonance imaging (MRI) data, Oeppen et al[58] demonstrated that the most common injuries after acute trauma of the knee joint were chondral in nature. Still, osteochondral joint surface defects are more common in adolescents than in adults.

Because adult hyaline cartilage is divided into calcified and noncalcified layers, trauma-related shearing forces typically result in a chondral fracture. Among children and adolescents, calcification has not set in; this leads to trauma force being transmitted directly into the subchondral bone. Therefore, osteochondral lesions are more common. Traumatic cartilage lesions often occur simultaneously with other knee abnormalities, such as meniscal tears, ligament ruptures, and, most commonly, acute lateral patellar dislocations, in which osteochondral fractures are reported in 25% to 75% of cases. In a large Finnish cohort that was observed over a 2-year period, an annual incidence of acute patellar dislocations of 44 per 100,000 in children aged 0 to 16 years was reported. In the same population, the incidence in children aged 9 to 15 years increased to 107 per 100,000.[56] The majority of patients reported a twisting mechanism or injury during sporting activities.

In 2013, Seeley et al[73] reported outcomes after an acute patellar dislocation for a cohort of 46 patients with a mean age of 14.6 years (range, 11-18 years). Osteochondral fractures of the patella occurred in 35 patients (76%), the lateral femoral condyle was involved in 11 patients (24%), and both locations were involved in 3 patients (6.5%). Twenty-six patients (68%) subsequently underwent surgery after their injury. An injury to the medial patellofemoral ligament (MPFL) was identified on MRI in 97.8% of patients (45/46). Six patients required arthrotomy, 6 patients underwent arthroscopic surgery, and 14 underwent a combination of procedures. Open reduction internal fixation was performed in 6 cases: 4 lateral femoral condyle lesions and 2 patellar lesions. The majority of patients (13/18) who underwent nonoperative management for a patellar osteochondral injury had lesions <1 cm in diameter. Loose body removal was performed in 20 (43.5%) patients. Eight of those patients underwent isolated loose body removal, whereas 12 patients were treated with concomitant loose body removal and medial structure surgery. Isolated loose body removal was performed in 5 cases for irreparable patellar osteochondral fractures and in 3 cases for irreparable femoral lesions. Fifteen patients (32.6%) underwent concomitant medial repair at the time of surgery. Patients with patellar osteochondral injuries reported higher IKDC scores on average than those with lateral femoral condyle injuries at 1 year postoperatively (91.12 vs 72.13, respectively; $P < .003$).[73]

Generally speaking, it should be the goal of the treating physician to analyze the underlying lesion by MRI and/or radiograph, treat coexisting abnormalities (eg, patellar instability), and aim to reattach the flake fragment (using pins or screws)[8] whenever possible within a short time period, as proposed in a 2011 French multicenter study.[18] Using nonresorbable material on the patellar undersurface makes subsequent removal through a second arthrotomy procedure necessary. In this regard, we recommend the use of absorbable material to refix patellar osteochondral flakes. On femoral condyles, and this is particularly true for OD lesions, metal or titanium screws are more frequently used. Increased compression can be applied to the fracture gap, and secondary removal can easily be performed in an arthroscopic setting.

Absorption processes within bone and cartilage may cause subsequent problems with any kind of fixation device. Prominent screws, especially nonabsorbable ones, may induce secondary cartilage damage to the opposing joint surface. We prefer absorbable material for all traumatic and reparable (reattachment) fragments, independent of the location. Both material types are being applied for OD lesion refixation. When extensive subchondral bone repair is required and/or the fragment is large and may require a certain mechanical compression, 2.0 titanium screws are preferred to generate safe mechanical stability. Using this technique, screw heads must be minimally sunk in relation to the surrounding cartilage to prevent collateral damage.

In some cases, the dislocated fragment does not contain a bony layer underneath the cartilage. Refixation cannot be recommended in these cases. Discarding the fragment and simply debriding the defect can be considered for very small and/or nonweightbearing regions, with the added benefit of quicker rehabilitation. Alternatively, the cartilage fragment can be cut/minced into multiple small pieces and retransplanted into the defective cartilage, for example, by using fibrin glue and/or collagen membranes/matrices. This technique was first reported in the early 1980s, and good clinical outcomes were recently published.[2,11,19] Autologous high-quality tissue is applied during 1-step surgery without causing donor site morbidity.[12] Standard operative techniques (described below) are used to treat cartilage defects when refixation or mincing procedures are not feasible.

The goal of surgical management for traumatic osteochondral flakes should be to retain the native tissue whenever possible and simultaneously treat the underlying lesion (eg, patellar stabilization).

DEGENERATIVE JOINT SURFACE ABNORMALITIES

With the exception of OD lesions, degenerative joint surface abnormalities are highly uncommon among children and adolescents. Juvenile rheumatoid arthritis is capable of inducing early joint degeneration. Juvenile idiopathic arthritis (JIA) is defined as arthritis of an unknown cause with an onset before the age of 16 years, persisting for more than 6 weeks. JIA is the most common chronic childhood rheumatic disease, with a reported prevalence of 16 to 150 per 100,000 in high-income countries. Juvenile arthritis is classified according to 7 different categories based on clinical features (ie, the number of joints involved), family history, and laboratory markers.

The clinical care of children with JIA has improved tremendously over the past years. The goal of treatment for JIA is to obtain total suppression of joint inflammation. The first-line treatment consists of nonsteroidal anti-inflammatory drugs and intra-articular steroid injections. It is often followed by methotrexate and, in resistant cases, by biologic therapy such as TNFα modulators. Kroger and coworkers[36] reported that osteochondral lesions are frequently found in patients suffering from JIA, concluding that MRI is advocated particularly among patients with persistent pain, swelling, and locking symptoms. Patients with post–septic arthritis may have signs of premature degeneration including chondromalacia. However, children and adolescents are very infrequently affected by such conditions.

Morbidly obese children and adolescents often suffer from knee and hip pain due to weight-associated cartilage wear, resulting in altered bone proportions. Interestingly, Widhalm and coworkers[83,84] demonstrated an association of pain and early cartilage lesions in an MRI-based study. In 38 of 39 morbidly obese children and adolescents, a marked cartilage lesion could be shown in at least one region of the knee. Clinical symptoms were significantly correlated to the number of cartilage lesions.[83,84]

Finally, emerging evidence suggests that genetic components may contribute significantly to OA pathophysiology. Genome-wide linkage analyses have identified selected chromosomal loci that are associated with a significantly increased predisposition for primary OA: OA susceptibility genes. Siblings of patients undergoing hip and knee replacement surgery have a 2- to 3-fold increased risk of developing OA, with a 27% severe OA heritability rate.[17] Genes linked to the prevalence and progression of OA include those belonging to the bone morphogenetic protein and the Wnt signaling pathways. In human genetic studies, Chapman and Valdes[15] have identified components, such as the bone morphogenetic protein GDF5, as being important in joint abnormalities. Furthermore, genome-wide association studies have uncovered a variant in the MCF2L gene as significantly associated with large-joint OA.[15]

OA is not initiated by one defective gene but a combination of genetic disposition and environmental factors. Predisposition for the development of premature OA may not affect children and adolescents. Yet, predictive genomic DNA profiling would aid in sports selection and the establishment of personalized training and nutrition programs. An increased use of genomic DNA profiling would not detect or determine superior athletic performance. It may predict abilities and weaknesses associated with sports performance while detecting low penetrance sequence variations not proven to be causative but probably contributory to the relevant phenotypic manifestations.

Degenerative articular cartilage defects are highly infrequent among children and adolescents. Rheumatoid

arthritis, obesity, and genetic predisposition may be causative for premature degeneration within this population.

OSTEOCHONDRITIS DISSECANS

OD of the knee is traditionally regarded as an idiopathic, acquired, localized lesion of the subchondral bone. It may secondarily progress to involve the overlying cartilage surface. It is commonly seen among athletically active young children and adolescents. It occurs in approximately 15 to 29 cases per 100,000 athletes. The origin of OD has been an ongoing matter of debate, and a variety of pathophysiological pathways have been proposed. Despite several attempts to elucidate the origin and pathophysiology of OD, no concept has been universally accepted. Genetic contribution, ischemia, trauma, or a combination of these factors has been proposed as etiological origins.

Overuse can be paralleled by vulnerable subarticular bone, resulting in a defective bony region with a subsequent stress fracture. Persistent loading of this injured area may delay healing, resulting in a localized area of avascular necrosis that may progress to nonunion and fragment separation. Yet, Krause and coworkers[35] showed that the subchondral bone of International Cartilage Repair Society (ICRS) grade 1, 2, and 3 OD lesions was vital in a cohort of 64 patients (mean age, 11.4 years), 34 of whom required surgery because of lesion instability (11 histological specimens) for failed nonoperative treatment. The authors concluded that ischemia leading to avascular osteonecrosis is not a predominant etiological feature of OD. As a secondary finding, histological analysis revealed osteoidosis in early-stage OD lesions, and it was speculated that a lack of mineralization makes the bone segment more susceptible to mechanical stress, resulting in subchondral insufficiency fractures. Furthermore, the same study hypothesized that vitamin D deficiency correlates with the development of OD lesions.[35]

It has been reported that OD lesions are related to increased (sporting) activity. However, in many cases, these lesions are seen in sedentary children or children with average athletic participation. Most commonly, OD lesions are seen in the femoral condyles of the knee, usually the posterolateral aspect of the medial femoral condyle (50%-80%), which represents a watershed area for vascularity. Available demographic data have reported male predominance (2:1) and a substantial incidence of bilateral lesions (25%).[79]

Staging systems are based on radiographic, MRI, or arthroscopic appearance. Bruns[13] divided lesions into stable or unstable with intact or pathological overlying cartilage. Interestingly, current classification systems commonly focus on the bony abnormality in isolation, without consideration of the overlying articular cartilage layer. The sclerotic zone beneath the articular cartilage plays an important pathophysiological role with regard to the invasiveness of subchondral bone repair (eg, retrograde drilling vs open cancellous bone plasty).[66] According to the ICRS, grade 1 is a stable lesion in continuity with the host bone covered by intact cartilage; grade 2 is stable on probing with partial discontinuity of the lesion from the host bone; grade 3 is unstable on probing with the fragment not dislocated and complete discontinuity of the "dead in situ" lesion; and grade 4 is a dislocated fragment.

A large body of evidence exists regarding the management of OD lesions, but there is no consensus on optimal treatment.[1,69] Our current practice proposes conservative management for grade 1 lesions as well as for asymptomatic grade 2 lesions.[81] Symptomatic grade 2 lesions as well as grade 3 and 4 lesions indicate operative treatment. Yet, selected cases have to be treated individually when patients suffering from grade 3 to 4 lesions remain without symptoms. Given that these patients are young and have a strong regeneration potential, conservative treatment can be initiated after discussing the risk for failure and subsequent indications for surgery in the future. Repetitive MRI must be scheduled.[31]

Nonoperative management focuses on activity modification and the cessation of sports and impact activities for 3 months in support of a physical therapy program. Vitamin D blood values should be normal. Retrograde drilling is indicated for symptomatic stable (arthroscopic probe testing) grade 2 lesions. Activation of the deep subchondral bone (antegrade "vitality" drilling), cancellous bone grafting, and refixation of the fragment (including debridement of the fragment bony retrosurface) are options when the cartilage layer is intact in grade 3 lesions. For dislocated grade 4 lesions, a similar treatment regimen to that used for grade 3 lesions can be pursued because the fragments have been shown to have comparable chondrocyte viability as well as differentiation potential with the surrounding undamaged cartilage.[61,68] Loose cartilaginous tissue can also be used for secondary ACI.[23]

When the cartilage layer is destroyed and/or not suitable for preservation, it needs to be replaced using standard cartilage repair techniques. Existing bony lesions must be addressed simultaneously. This constellation is most often found in grade 4 lesions but can also be present in grade 3 lesions. For small lesions (up to 1 cm^2), the microfracture technique can be used because it also stimulates the subchondral bone. In larger lesions, either osteochondral cylinder transplantation, repairing both bone and cartilage at once, or "sandwich-type" ACI with underlying cancellous bone grafting is indicated. Because unvital bony tissue must be replaced during subchondral repair, we propose to always apply autologous bony tissue to directly generate vitality in the osseous defect. This tissue can be harvested from the proximal tibia and distal femur using the same approach or from the tibia or iliac crest via an additional approach in cases in which larger bony defects are repaired.

Many other alternatives and bone graft harvest locations can be applied. The use of cylinders or osteochondral blocks from the iliac crest may provide stronger initial biomechanical stability compared with compacted cancellous grafting. Alternative techniques such as bone marrow aspirate concentrate (BMAC), augmented microfracture, or empty membranes can be considered; however, published evidence for juvenile patients is sparse, and they are thus not recommended at the moment. We clearly prefer the sandwich technique over osteochondral cylinders because the

defective chondral area is covered completely, while gaps may remain when multiple plugs are required. The transplant attaches to the surrounding cartilage with reduced donor site morbidity.[9] Furthermore, OD lesions have been described in the literature to result in optimal outcomes after ACI when compared with other indications for ACI treatment. Ochs and coworkers[57] reported good clinical success and simultaneous remodeling processes of articular cartilage repair tissue as well as subchondral lamina using the sandwich technique.

In 2014, the outcomes after OD surgery were summarized by Abouassaly et al[1] in a systematic review including 25 studies with 470 patients aged under 18 years (516 lesions). Operative techniques included, for stable lesions, arthroscopic and open transarticular drilling, either alone (41%) or with bioabsorbable pin fixation (3%), extra-articular drilling (29%), and fixation with bioabsorbable screws (4%) or bone pegs (4%). For unstable lesions, surgical techniques included arthroscopic and open fixation with bioabsorbable pins (9%), metal screws (4%), bone pegs (4%), osteochondral plugs (3%), or bioabsorbable screws (2%) as well as transarticular drilling with bioabsorbable pin fixation (3%) and drilling with metal screw fixation (2%). The most common techniques were transarticular drilling for stable lesions and bioabsorbable pin fixation for unstable lesions. The key findings were that the vast majority of lesions healed postoperatively, regardless of the technique, and that high-quality trials are required to more appropriately compare the effectiveness of respective techniques.[1] Clear factors that are associated with an increased failure rate after nonoperative management are larger lesion size, skeletal maturity, and lesion instability.

Ramirez et al[66] reported that lesions without sclerosis at the cartilage-to-bone interface show a tendency toward spontaneous recovery with conservative treatment in a cohort of 85 patients. Lesions with perilesional sclerosis perform worse in a natural course.[66] Kramer and coworkers[32] recently reported outcomes after the treatment of patients with patellofemoral OD. The authors reported that surgical treatment of patellofemoral OD in children and adolescents produces a high rate of satisfaction and return to sports. Male patients and trochlear lesions were more common, the mean tibial tuberosity–trochlear groove distance on MRI was elevated in comparison to historical controls, and the use of fixation was the only predictor of reoperations. Female sex, prolonged duration of symptoms, and internal fixation were associated with worse outcomes. Most patients were able to return to sports, and postoperative imaging showed high rates of incomplete healing that was not associated with clinical outcomes.[32]

OD lesions represent the major degenerative cartilage knee joint abnormality among children and adolescents. Highly differentiated as well as clearly stage-oriented treatment must be initiated. When intraoperative findings allow fragment retention, drilling or reattachment plus subchondral bone management defines the optimal treatment modality. However, standard cartilage repair techniques result in the best postoperative outcomes in patients with OD when compared with other abnormalities.

TABLE 2
Treatment Principles for Chondral and Osteochondral Defect Repair in the Knee Joint Among Children and Adolescents

With the exception of fresh traumatic flakes, conservative therapy should be first-line treatment of symptomatic defects to the joint surface.
Standard cartilage repair techniques are recommended to surgically treat symptomatic International Cartilage Repair Society grade 3 or 4 lesions.
Standard cartilage repair techniques are microfracture, osteochondral cylinder transplantation, and autologous chondrocyte implantation.
The technical application should be evaluated by cartilage defect diameter, subchondral bone deficiency, and defect localization.
The joint surface defect size has to be considered with relation to overall knee joint dimensions; the treatment modality has to be adapted accordingly.
Marrow stimulation procedures as well as osteochondral cylinder transplantation are not recommended for the patellar undersurface.
Retainment of osteochondral flakes via refixation/reattachment should be the desired goal in fresh traumatic lesions.
Osteochondritis dissecans defects are operatively treated by retrograde drilling, fragment reattachment plus subchondral bone repair, or standard cartilage repair techniques when preservation is impossible.
Any concomitant or coexisting abnormality has to be treated simultaneously with the desired/executed joint surface repair.

CONSERVATIVE VERSUS OPERATIVE TREATMENT

In the young patient population, and particularly in children, surgical indications should be cautiously evaluated (Table 2). Sequential intra-articular surgical manipulation may be detrimental for the patient in following years.[78] Adapted activity, patience, and inherent regeneration potential are the most important factors to be considered during nonoperative treatment. This constellation must be intensively discussed with the patient and often family members to generate an optimal treatment. We propose treating children and adolescents suffering from knee joint cartilage defects (fresh flake trauma excluded) by conservative means initially for at least 3 months. This is particularly true for patients with a short symptom duration. Patients who report a long history of symptoms should be managed more individually because symptom duration also has a major impact on long-term success among children and adolescents.

Aside from OD evidence,[7] there is, to the best of our knowledge, no published evidence on the outcomes of nonoperative chondral/osteochondral knee joint treatment in children and adolescents. Yet, certain circumstances clearly pave the way for an operative intervention. Clinical symptoms as reported by the patient should be regarded as the indicator for operative versus conservative management. Particularly among children and adolescents, surgical treatment should be avoided when the patient is

asymptomatic. The other major reference for surgical indications is defined by lesion morphology on MRI. Surgery is indicated when the lesion can be described as grade 3 or 4 according to the ICRS classification system.[80] There are no clear guidelines as to when and which surgical treatment should be initiated according to the lesion diameter. Different groups have proposed adult algorithms according to lesion diameter and patient activity.[52,53] Among children and adolescents, we propose defining anything up to 2 cm^2 as small diameter and anything larger than 2 cm^2 as large diameter. When a grade 3 or 4 cartilage defect is visible on MRI and the patient is symptomatic after failed conservative management, size does not matter.

It is important to distinguish the correct surgical technique to apply. In general, the 3 classic cartilage defect repair techniques—microfracture, osteochondral cylinder transplantation, and ACI—are available for children and adolescents.[29] All other products and techniques do not have a long enough track record and/or published evidence to recommend surgical application in these cases. We advocate microfracture in a lesion with a diameter of up to 2 cm^2 with intact subchondral bone or only minimal deficiency. Microfracture of the patellar undersurface should be avoided in general. It is recommended to avoid traditional awls in favor of small-diameter K-wires or drills (1.0-1.6) because Orth and coworkers[59] have shown in a large animal model that smaller awls provoke improved healing when compared with larger awls. Reasons may be less trauma and compression to the bone surrounding the hole and better access to the cancellous bone with more and better quality stem cells.[6]

In small-diameter osteochondral lesions with clearly defective subchondral bone (>3- to 5-mm bony deficiency), osteochondral transplantation may provide a surgical option with 1-step replacement of bone and cartilage and a rather swift regeneration process.[26] The application of only 1 cylinder should be the goal of surgical treatment to avoid a cobblestone pattern of the articular surface with fibrous tissue between cylinders. The dorsomedial condyle constitutes an attractive location to harvest cylinders. For all large-diameter chondral and osteochondral lesions, we recommend ACI and/or cancellous bone grafting because this technique provides the greatest biological potential and is substantiated by very strong scientific evidence not only among adult patients.[71] Advanced ACI techniques can be performed under arthroscopic settings without harm to the surrounding cartilage.[74] When treating children and adolescents with ACI, one has to consider local guidelines for cell-based treatment methods because they may be for off-label use.

There are multiple novel and alternative techniques available to treat defective cartilage. They are primarily intended for adults, and current published evidence has to be considered very light.[29] Further evidence on novel products must be generated to evaluate whether they are potentially applicable for children and adolescents. Until then, we propose using the traditional methods to repair defective cartilage. However, using concentrated BMAC should be considered as an elegant alternative to ACI for the treatment of large-dimension cartilage defects in children and adolescents.[50] The greater number of MSCs, as well as the strong plasticity of young patient MSCs, may enhance the efficacy of BMAC in skeletally immature patients.[22] Gobbi et al[24,25] have reported satisfying outcome data using BMAC in adult patients. The technique is a 1-step procedure and does not require in vitro cell culture (as in ACI) and is therefore much more economic.

The classic cut-off point to switch from marrow stimulation techniques (microfracture) to cell-based repair techniques has been most often described to be somewhere between 2 to 3 cm^2. This can be partially transferred to children and adolescents; however, general knee joint dimensions are not comparable with the adult counterparts.[27,62] Logically, the localized cartilage defect's lesion diameter may have more significance when it is matched with the remaining joint surface. It is justifiable that symptomatic low-diameter lesions of ICRS grade 3 or 4 can be initially treated by conservative means. Thereby, the patient must be closely monitored clinically as well as with imaging. In addition, physical activity needs to be temporarily adapted, while the defective joint's mobility and strength are maintained via conservative measures such as physical therapy. When circumstances allow, the managing physician should aim to avoid surgical intervention, which can have significant detrimental effects on further childhood development, including psychological aspects.[21]

Selected patients with obvious symptoms, ICRS grade 3 or 4, and failed conservative pretreatment are clear indications for an operative approach. Also, coexisting trauma-related cartilage defects seen or diagnosed with a concomitant soft tissue injury (eg, ACL rupture) should be treated accordingly during the same surgical setting. ACL reconstruction–related intra-articular hematomas are rich in growth factors that are beneficial for the generation of cartilage repair tissue after microfracture performed at the same time as ACL replacement.[28]

Chronic symptomatic ICRS grade 3 or 4 joint surface defects should be conservatively managed, and adapted activity should be the first-line treatment modality with close clinical monitoring and imaging (MRI). In cases of failed conservative treatment, a defect- and patient characteristics–oriented approach (Table 3) has to be tailored to treat the patient effectively and early after the onset of symptoms.

CONCOMITANT ABNORMALITIES

Soft tissue knee joint injuries such as an ACL rupture, patellar dislocation, meniscal lesion, or tibial spine fracture very often coincide with chondral or osteochondral abnormalities.[34] The soft tissue injury needs to be addressed accordingly to protect the applied cartilage repair. ACL tears in pediatric and adolescent patients are no longer considered a rare entity. The rate of ACL injury diagnoses and reconstructions in both pediatric and adolescent patients is rising significantly more quickly than in adults.[82]

Current evidence suggests that ACL-deficient children and adolescents should undergo surgical stabilization.[67]

TABLE 3
Chondral and Osteochondral Defect Dimensions and Recommended Operative Treatment Modality

Small lesions are regarded as <2 cm^2.
Large lesions are regarded as >2 cm^2.
Chondral lesion <2 cm^2: microfracture.
Chondral lesion >2 cm^2: autologous chondrocyte implantation.[a]
Osteochondral lesion <1.5 cm^2: osteochondral cylinder transplantation.[b]
Osteochondral lesion >1.5 cm^2: autologous chondrocyte implantation plus subchondral bone grafting.
With respect to frequent subchondral bone abnormalities, particular attention has to be paid to this region.
Marrow stimulation procedures as well as osteochondral cylinder transplantation are not recommended for the patellar undersurface.

[a]Alternative cell-based techniques may be applied (particularly in the future).

[b]It should be the goal to use a maximum of 2 osteochondral cylinders when this technique is performed to minimize donor site morbidity and to avoid a "cobblestone" pattern at the recipient site.

Pediatric and adolescent patients undergoing ACL reconstruction have a significantly increased incidence of concomitant meniscal and cartilage procedures. Newman et al[51] investigated factors that contribute to the prevalence and severity of concomitant chondral and meniscal injuries among patients aged 14 to 19 years versus those aged <14 years at the time of ACL reconstruction. Among patients undergoing surgery more than 3 months after their initial injury, the odds of chondral and/or meniscal injuries requiring additional operative procedures were 4.75 (95% CI, 1.70-14.37; $P = .0027$) times the odds of additional procedures among patients undergoing surgery less than 3 months after their initial injury. There was a high rate of coexisting chondral lesions. However, there was no significant difference in the prevalence of chondral injuries that did or did not require additional operative procedures in the older (31.6%) versus younger (21.2%) cohort ($P = .1073$).[51]

Others have also reported that increased time intervals between an ACL rupture and repair highly increase the number of chondral and meniscal injuries that need to be repaired.[46] Early treatment is recommended for unstable joints and athletically active patients to protect the joint in terms of OA.[76] In the event of an acute lateral patellar dislocation, with or without osteochondral lesions, a rupture of the MPFL is the underlying abnormality. Most patients develop subjective instability of the patella as a consequence. Many suffer from concurrent patellofemoral chondral defects. Immediate surgical treatment is often necessary because of large osteochondral fragments. In this population of patients, an additional patellar stabilization procedure is highly recommended to interrupt the underlying abnormality and to prevent the development of chronic patellar instability. Patients who develop chronic instability plus underlying joint surface defects should also be treated with both patellar stabilization and cartilage surface repair. In the highly complex patellofemoral joint, many additional abnormalities such as valgus deformity, patella alta, trochlear dysplasia, or pathological tibial tuberosity–trochlear groove distance can be encountered and potentially have to be addressed accordingly.

Siebold and colleagues[75] have reported satisfying outcomes when combining MPFL plasty and surface repair (ACI) as one example for appropriate treatment when a ruptured MPFL is the major factor for instability. There are currently no published reports on coexisting isolated meniscus and cartilage defects in the knee joint with a general satisfactory healing potential of meniscal ruptures among children and adolescents.[33] Mitchell and coworkers[42] reported coexisting abnormalities after an anterior tibial spine fracture in a cohort of 58 children; 59% of children with an anterior tibial spine fracture had an associated soft tissue or other bony injury diagnosed by MRI or arthroscopic surgery. The most prevalent associated injuries were meniscal entrapment, meniscal tears, and chondral injuries. There was no meniscal or chondral injury associated with type I fractures. Twenty-nine percent of type II injuries demonstrated meniscal entrapment, with 33% showing meniscal tears. Seven percent demonstrated a chondral injury. Forty-eight percent of type III fractures had entrapment, whereas 12% showed meniscal tears. Eight percent had a chondral injury.[42]

A leg deformity is not as frequently coexistent to chondral and osteochondral abnormalities as it is among adults. Yet, it should always be considered and evaluated because it has been shown to be a very effective surgical adjunct when treating degenerative cartilage defects among adults.[10] The published outcomes after hemiepiphysiodesis for the treatment of angular deformities of the lower extremity are weak. Such deformities, though, should be considered early prearthritic factors. During childhood and with remaining growth, guided growth offers an elegant solution for this problem. Resulting in temporary hemiepiphysiodesis, the 8-plate procedure offers an alternative technique to Blount staples and definitive epiphysiodesis.[55] Radiological parameters must be gathered carefully to achieve physiological correction.[64]

Underlying or concomitant abnormalities have to be diagnosed and addressed with sensitive attention to provide optimal healing circumstances for simultaneous cartilage defect repair.

OUTCOME STUDIES

The reported outcomes after operative cartilage repair in the knee joint in children and adolescents are sparse in general (Table 4). With exceptions,[26] high-quality, that is, level of evidence 1, studies are unavailable. A recent systematic review including a total of 13 studies with level 1 (1 study), level 2 (2 studies), and level 4 (10 studies) evidence and a total of 285 pediatric patients reported a mean modified Coleman Methodology Score of 63.5 (fair quality). The most common methodological limitations within studies were the study design, sample size, and length of follow-up. The authors concluded that the quality of available literature is poor and that there is a lack of comparative trials.[16]

TABLE 4
Outcome Studies on Chondral and Osteochondral Defect Repair Among Children and Adolescents in the Knee Joint

Published evidence on cartilage repair is weak.
Clinical outcomes of standard cartilage repair techniques are considered satisfying.
Selected trials have reported superior outcomes in comparison with adult patients.
Previous surgery and symptom duration are the 2 main factors to influence/predict clinical outcomes.
Return to the preinjury sports activity and level is correlated with shorter preoperative symptoms and a lower number of prior surgery.
Microfracture results in inferior outcomes with increasing defect size.
Microfracture results may deteriorate over time.

In 2015, Steadman et al[77] reported the outcomes after microfracture for full-thickness cartilage defects of the knee in adolescents with an average follow-up of 5.8 years (range, 2.0-13.3 years). The cohort consisted of a total of 26 patients (14 female, 12 male). The average age was 16.6 years (range, 12.0-18.9 years). Ninety-six percent of lesions were patellar (37%) or femoral condyle defects (medial 26%, lateral 33%). The average postoperative Lysholm score was 90 (range, 50-100). The median Tegner score was 6 (range, 2-10). Median patient satisfaction with the outcome was 10 (range, 1-10). One patient underwent revision microfracture. The authors concluded that adolescent patients who underwent microfracture for the treatment of full-thickness knee chondral defects demonstrated increased activity levels and excellent function after surgery.[77]

Similar results were reported earlier by Salzmann and coworkers.[70] In their study, a total of 10 patients (2 female, 8 male) were analyzed with an average follow-up of 3.5 years. The average patient age at the time of surgery was 14.1 ± 2.3 years. The average symptom duration, known as one major factor to affect clinical outcomes, was 12.1 ± 13.1 months. All cartilage defects were single lesions (3 medial femur, 2 lateral femur, 2 trochlea, 2 patella, 1 lateral tibial plateau) with an average defect size of 1.2 ± 0.8 cm^2. The average postoperative Lysholm score was 92.1 ± 9.9, the average IKDC score was 90.4 ± 8.2, and the average Tegner score was 7.0 ± 1.9. The clinical outcomes differed across knee joint regions (best outcomes in the lateral femur and worst outcomes in the patellar undersurface) as well as in nonsignificant variations in preoperative symptom duration (better outcomes with shorter symptom duration). There were no treatment failures. The authors compared the young cohort of patients with a cohort of older patients (n = 444) who had undergone microfracture as well and identified significantly better clinical outcomes among children and adolescents.[70]

Micheli et al[41] reported the outcomes of a study cohort of 37 patients (mean age, 16 years) averaging 4.3 years after ACI (mean cartilage defect size, 5.4 cm). Twenty-three patients underwent at least 1 cartilage repair procedure before the cartilage harvest, including 11 who underwent a marrow stimulation procedure. After an average follow-up of 4.3 years, the mean changes in scores on 10-point scales of the Cincinnati Knee Rating System measuring overall condition, pain, and swelling were 3.8, 4.1, and 3.4 points, respectively. One patient underwent implantation that failed. The authors concluded that ACI may be an effective option for children and adolescents with large symptomatic chondral lesions of the distal femur.[41]

Comparable results were reported in 2005 on 22 patients who were treated with ACI with a focus on return to sporting activity; 96% of adolescents reported good or excellent results with significant increases in the postoperative Tegner activity score and Lysholm score.[44] Ninety-six percent returned to high-impact sports and 60% to an athletic level equal or higher than before the knee injury. Return to preinjury sports correlated with shorter preoperative symptoms and a lower number of prior surgeries. All adolescents with preoperative symptoms ≤12 months returned to preinjury-level athletics, compared with 33% with preoperative intervals longer than 12 months.[44]

Macmull et al[40] reported the outcomes of 31 patients with an average age of 16.3 years after chondrocyte implantation (24 ACI, 7 matrix-induced ACI) at a mean follow-up of 66.3 months. Clinical outcomes revealed that 84% of patients achieved excellent or good results. Biopsy results revealed hyaline cartilage in 24% of cases, mixed fibrous/hyaline cartilage in 19%, and fibrocartilage in 57%. The authors stated that in comparison with studies in adult patients, higher success rates were attained.[40] Just recently, DiBartola et al[20] summarized the outcomes of ACI in a systematic review of 5 studies with 115 patients (mean follow-up, 52.3 months; mean defect size, 5.3 cm^2) and discovered a mean postoperative clinical outcome score of 72.7% (37% preoperatively). Graft hypertrophy was the most common complication at 7%. The authors concluded that cartilage repair in adolescent knees using ACI provides success across different clinical outcome measures. The only patient- or lesion-specific factor that influenced clinical outcomes was shorter duration of preoperative symptoms.

Murphy et al[49] reported the outcomes of 39 pediatric (mean age, 16.4 years) patients who underwent fresh osteochondral allograft transplantation for the treatment of chondral and osteochondral lesions of the knee joint with an average follow-up of 8.4 years in 2014. Most of the knee joints (79%) had undergone at least 1 previous surgery. The most common underlying causes of the lesions were OD (61%), avascular necrosis (16%), and traumatic chondral injury (14%). The mean allograft size was 8.4 cm^2. Five knees experienced clinical failure at a median of 2.7 years (range, 1.0-14.7 years). Four failures were salvaged successfully with another osteochondral allograft transplantation. One patient underwent prosthetic arthroplasty 8.6 years after a revision allograft procedure. Graft survivorship was 90% at 10 years. Of the knees whose grafts were in situ at the latest follow-up, 88% were rated good/excellent (18-point scale). The mean IKDC score improved from 42 preoperatively to 75 postoperatively, and the Knee Society function score improved from 69 to 89 (both $P < .05$). Eighty-nine percent of patients reported being extremely

satisfied or satisfied.[49] Miura et al[45] and Sasaki et al[72] described comparable outcomes in their respective cohorts of patients with OD who were all treated by autogenous osteochondral plugs. Yet, these patients had fewer failures compared with the allograft patients who were analyzed by Murphy et al.[49]

In 2009, Gudas and colleagues[26] compared the outcomes of arthroscopic mosaic-type autologous osteochondral transplantation and microfracture procedures for the treatment of OD defects of the femoral condyles in a randomized controlled trial. A total of 50 children with a mean age of 14.3 years (range, 12-18 years) were followed up at an average of 4.2 years after surgery. While the postoperative function was satisfying and similar 1 year after surgery, there was deterioration at 4 years postoperatively within the microfracture group, with a significant difference in clinical outcomes compared with the osteochondral cylinder group, with still encouraging clinical results for children under the age of 18 years.[26] This trend has been very well investigated among adult patients.[43]

Chawla et al,[16] in a 2015 systematic review of the literature on pediatric patients treated for knee joint cartilage defects, concluded that microfracture, osteochondral transplantation (autograft and allograft), and ACI have all been implemented successfully in the pediatric knee. Microfracture was generally associated with poorer outcomes and shorter durability than the other techniques, particularly in larger lesions (>3 cm^2). The superiority of the other techniques was attributed to the more anatomic hyaline cartilage repair tissue that they formed compared with the less durable fibrocartilage tissue produced after microfracture. While microfracture is technically the simplest procedure, its selection as first-line therapy for chondral lesions in the pediatric knee can be questioned. However, the review by Chawla et al[16] could not answer the question of which alternative technique should be preferred, given the general low quality of the literature and lack of comparative trials.

Clinical outcomes after standard cartilage defect repair procedures in children and adolescents are satisfying and may be superior to the outcomes in adults. Current evidence cannot provide clear guidelines regarding defect dimensions. Yet, guidelines that have been proposed for adult cartilage defect repair can serve as an orientation. The application of standard cartilage repair techniques among children and adolescents appears to be safe and thus comparable with adult patients concerning this aspect. More frequent complications have not been reported. Complications with regard to a growing musculoskeletal system and applied cartilage repair procedures have not been reported, to the best of our knowledge. Thus, ACI can be recommended without limitations, particularly with regard to increasing defect dimensions. Similar drawbacks as in adult patients have been reported for microfracture (inferior outcomes with increasing lesion size and tissue deterioration over time). Particular attention has to be paid to subchondral osseous abnormalities. Such defects must be addressed rigorously to ensure successful overlying chondral repair or regeneration.

CONCLUSION

Children and adolescents are frequently involved in strenuous sporting activities. Potentially injurious consequences to the articulating joint surfaces are frequent and rising. Furthermore, many patients suffer from hereditary OD, which is potentially aggravated through activity. Degenerative joint diseases, rheumatic diseases, and septic arthritis are rather infrequent within this population. When existent, chondral and osteochondral lesions may present a highly severe condition affecting the joint as a whole. Because children and adolescents are actively growing, their inherent regeneration potential has been described to be more potent compared with their adult counterparts. For selected chondral and foremost osteochondral (including OD) lesions, conservative management is therefore clearly justified when strict monitoring is provided.

Larger, symptomatic, and advanced lesions clearly represent a surgical indication for which standard operative techniques are available to the treating surgeon. Surgical indications are comparable with adult patients, in whom lesion size and location are the 2 main components that determine treatment modalities. Coexisting or underlying abnormalities must be addressed during the same treatment process. With regard to regeneration potential, marrow stimulation techniques may be associated with enhanced outcomes and less deterioration in comparison with adult patients. Accordingly, treatment indications should be adjusted for children and adolescents. Large-diameter lesions require advanced surgical therapy such as ACI, which can be easily combined with cancellous bone grafting to address coexisting subchondral abnormalities if necessary.

Lesion size, previous surgery, and symptom duration are the major factors to affect final treatment outcomes. These predictors are also comparable with adult patients. Clinical function, satisfaction with surgery, and return to sports are overall satisfying and may be superior over adult patients. Yet, these populations have not been systematically compared. Chondral and osteochondral joint surface abnormalities represent serious health care events. Their management should be performed with extreme care to return the growing patient to previous activity and to prevent premature OA.

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