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INTERVIEW

SONJA VASIC

Champion of Europe & MVP of the FIBA Women's EuroBasket 2021

ASPIRE Publishing

TARGETED TOPIC Knee Joint Preservation


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THE EDITORIAL TEAM

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FROM OUR EDITOR

Five years ago, in the Aspetar Journal's first targeted topic on cartilage injury in sports, I started my editorial with:

«*As you receive this issue I hope you are enjoying a fantastic summer of sport, watching the pinnacle of sporting achievement – the Olympic Games – where many athletes will be accomplishing more and pushing themselves harder than any have before them, as they fight for a spot on the podium.*
I frequently ask myself though, what is the price these young champions will pay in the future, after their sporting careers are over? Often the answer to this question is "osteoarthritis".«

This year, during the Tokyo Olympic Games, our targeted topic is "Knee Joint Preservation" and we can state the following:

- Research studies still confirm that prevalence of OA (knee and hip) in retired elite athletes is between 28 and 60% compared to 12 to 15% in the general population.
- The restoration of damaged articular cartilage in athletes' knees remains one of the biggest challenges in sports surgery.
- Current treatment modalities have their benefits and shortcomings. Improvement of the existing techniques and innovative approaches are required to improve the results. Knowledge and understanding of the available surgical techniques is critical to the appropriate use of the intervention.

Since the last Olympic Games scientists, researchers, and clinicians have published numerous papers that research the problem of knee preservation. For that reason, I decided to return to this topic and re-examine how surgery and science share their insights on the pace of cartilage lesion treatment evolution. The goal of this targeted topic is to update our knowledge on what today's sports medicine providers need to know when assisting athletes with knee cartilage pathology.

Our guest editors, Dr Khalid Al-Khelaifi and Dr Manos Papakostas, have brought together Aspetar's surgical team, as well as Aspetar's visiting experts from all around the world for this targeted topic on Knee Preservation. Orthopaedic surgeon Dr Al-Khelaifi is one of the new generation of leaders in the field, with extensive clinical expertise and deep scientific knowledge. His colleague at the Aspetar Cartilage Centre of Excellence, Dr Papakostas, is an orthopaedic surgeon and former track and field athlete, who has a great passion for sports cartilage injuries.

I sincerely thank guest editors, Dr Al-Khelaifi and Dr Papakostas for their hard work that has made this outstanding issue, "Knee Joint Preservation", possible.

I also take this opportunity to thank Professor Mats Brittberg, who established "Aspetar Cartilage Centre of Excellence" 10 years ago, for his generous contribution of time and effort, through all these years, that made our cartilage project possible.

Finally, I draw your attention to the inspiring interview with FIBA's EuroBasket «Women Most Valuable Player of the Year 2021», Sonja Vasic. Kudos to the perfect interviewers, her Serbian countrywoman, Dr Lana Krzman, sports and exercise medicine specialist and former international basketball player herself.

Nebojsa Popovic MD PhD
Editor-in-Chief

FROM OUR GUEST EDITORS
CARTILAGE JOURNEY

Khalid Al-Khelaifi MD, FRCSC

Emmanuel Papakostas MD, FEBSM

The human bones join with each other in various ways to serve the functional requirements of the musculoskeletal system. The most critical function of all needs is purposeful motion. The effective interaction of all muscles, tendons, ligaments and articular cartilage defines the movement required from kicking a ball in a professional athlete to running and swimming and even walking. With a continuous repetitive movement, articular cartilage between bones helps the musculoskeletal system to move in the most efficient way. Without it, friction would consume the energy of this system and would put it incapable of making simple required actions.

The knee joint is incongruent, and it is the biggest incongruent joint in the human body. To accommodate incongruency, the joint itself has the highest thickness of articular cartilage among all joints. This indicates the importance of the articular cartilage in promoting the function of the joint.

Knee cartilage injury is a ravaging injury that can affect all people in all age groups. It is an irreversible injury that can progress with time to osteoarthritis, which is devastating to our patients.

Science and Orthopedics are evolving in this particular disease process. Our knowledge in basic science of cartilage cells allowed us to explore the option of stem cells in this disease. Arthroscopic advancement of knee surgery allowed us to have more sophisticated surgeries to this injury ranging from simple microfracture to Osteochondral allograft implantation depending on the size of the lesion. We started to understand the implication of mal-alignment and loss of the protection of the meniscus, and this lead us to correct these issues around the knee before tackling the cartilage injury.

Members of Aspetar surgical department, experienced in cartilage surgery, together with international experts are focusing on the current concepts of the treatment, in this Targeted Topic of the Aspetar Sports Medicine Journal.

An overview of the treatment algorithm is presented by Dr Papakostas. Dr Zikria gives us his advice and expertise on what skills a sports orthopedic surgeon needs to have in order to handle such injuries.

In the next group of papers, Dr Al-Khelaifi discusses diagnosis and treatment of osteochondritis dissecans, while Meniscus Allograft as treatment option is presented by Professor Verdonk. The role of alignment and its correction to decrease the load on cartilage is highlighted by Professor Seil.

Ultimately, in the last four papers the history of cell therapies together with the new era of orthobiologics is demonstrated. Professor Brittberg, one of the pioneers in cartilage restoration, focuses on the historical timeline of cartilage repair. Adipose tissue as source of "working" cells and its role in cartilage repair is discussed by Professor Sciarretta. Dr Slynarski, alongside with Dr Papakostas, introduces the latest development in combining chondrocytes and MSCs, as one-stage cartilage repair technique. Finally, the best evidence on the role of orthobiologics in cartilage treatment, specifically in osteoarthritis, is presented by Dr Filardo and the Bologna group.

I am sure that sport medicine clinicians will find these topics interesting and will benefit from the knowledge and expertise of this section editors and authors. I hope that the information that put forth is valuable to our readers.

Enjoy it!!

Best Regards,
Khalid & Mannos

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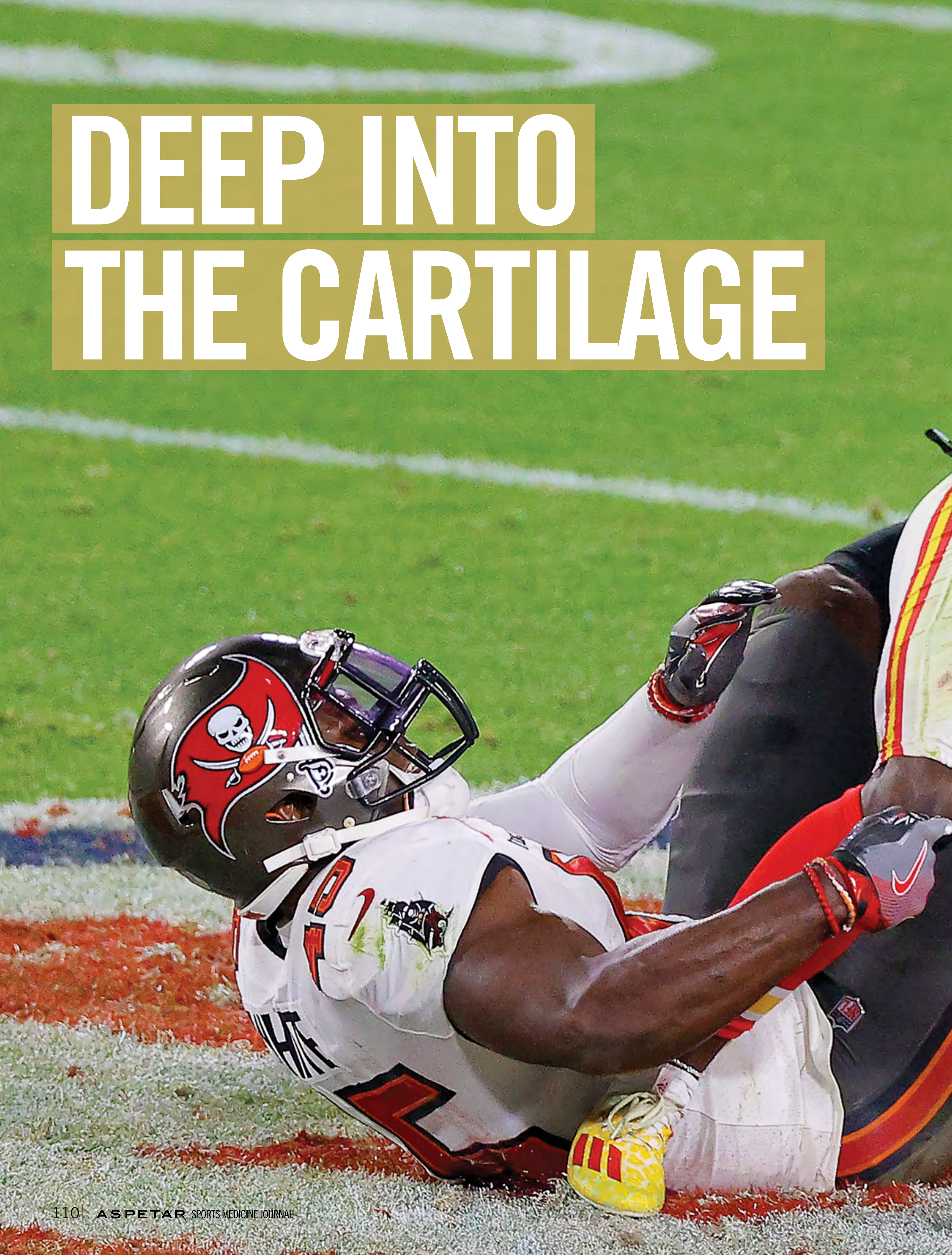
DEEP INTO THE CARTILAGE

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CARTILAGE INJURIES IN SPORTS

THE DILEMMA IS IN THE DETAIL

– Written by Emmanuel Papakostas and Pieter D'Hooghe, Qatar

Glossary:
AMIC – Autologous Matrix Induced Chondrogenesis,
BMS – Bone Marrow Stimulation,
BMAC – Bone Marrow Concentrate,
(M)ACI – (Matrix) Autologous Chondrocyte Implantation,
MSCs – Mesenchymal Stromal Cells,
OCA – Osteochondral Allograft,
OATS – Osteochondral Autologous Transfer,
PRP – Platelet Rich Plasma

INTRODUCTION

One of the most challenging practices in sports orthopedics and sports medicine is to treat musculoskeletal conditions that require a prolonged rehabilitation and a delayed return to play. A key example is the professional athlete suffering from a cartilage injury or pathology.

As sports medicine physicians, we are frequently confronted with debilitating cartilage injuries in our athletic population. The predominant reasons are:

- Increased participation in popular sports.
- Availability of imaging techniques like MRI.
- Increased incidence of surgery in athletes (such as ACL reconstruction and meniscal repair).
- High index of suspicion towards the pathophysiology of cartilage injury in the athlete.

CLINICAL DECISION MAKING

The athlete suffering from a cartilage lesion presents typically with pain, swelling, locking, catching or in a combination. Very often, this condition presents as a pseudo-instability and/or inability to move the articulation.

The etiology of the above symptoms is not always straightforward, but synovial inflammation caused by cartilage debris and inflammatory proteins are known to be key. Considering that cartilage is avascular and aneural, the presence of pain is a strong indicator of synovial inflammation and/or subchondral bone involvement. Additionally, mechanical symptoms (such as locking, catching, or pseudo-instability) are known to be linked with the intra-articular presentation of loose free bodies, cartilage flaps or exposed bone. The key to understanding why many athletes with MRI documented cartilage lesions are still able to engage in their sport, can be explained by the unique anatomical features of cartilage[1-3]. Current evidence shows that up to 14 % of athletes with cartilage lesions can present asymptomatic, even with full thickness lesions[1-5].

Especially in identified sports such as ice-hockey, volleyball, football and basketball[6-9], cartilage pathology can present as asymptomatic regardless of any loss of function or future surgical indication[10].

THE IDEAL PATIENT AND TREATMENT TIMING

In a systematic review, published in 2016, younger patients (with shorter preoperative duration of symptoms and without previous surgical interventions) were shown to have a better prognosis and earlier return to play after surgical treatment. Compliance to rehabilitation protocols and smaller size cartilage defects are also known to be positive prognostic factors[11].

Additionally, a systematic review in 2017 revealed that lesion size, athlete's age and concomitant surgical procedures are important predictors to consider as well12. On top of that, previous surgery was shown to be the single most predictive factor for return to the same sports level, together with younger age, traumatic lesions and absence of previous surgery[13].

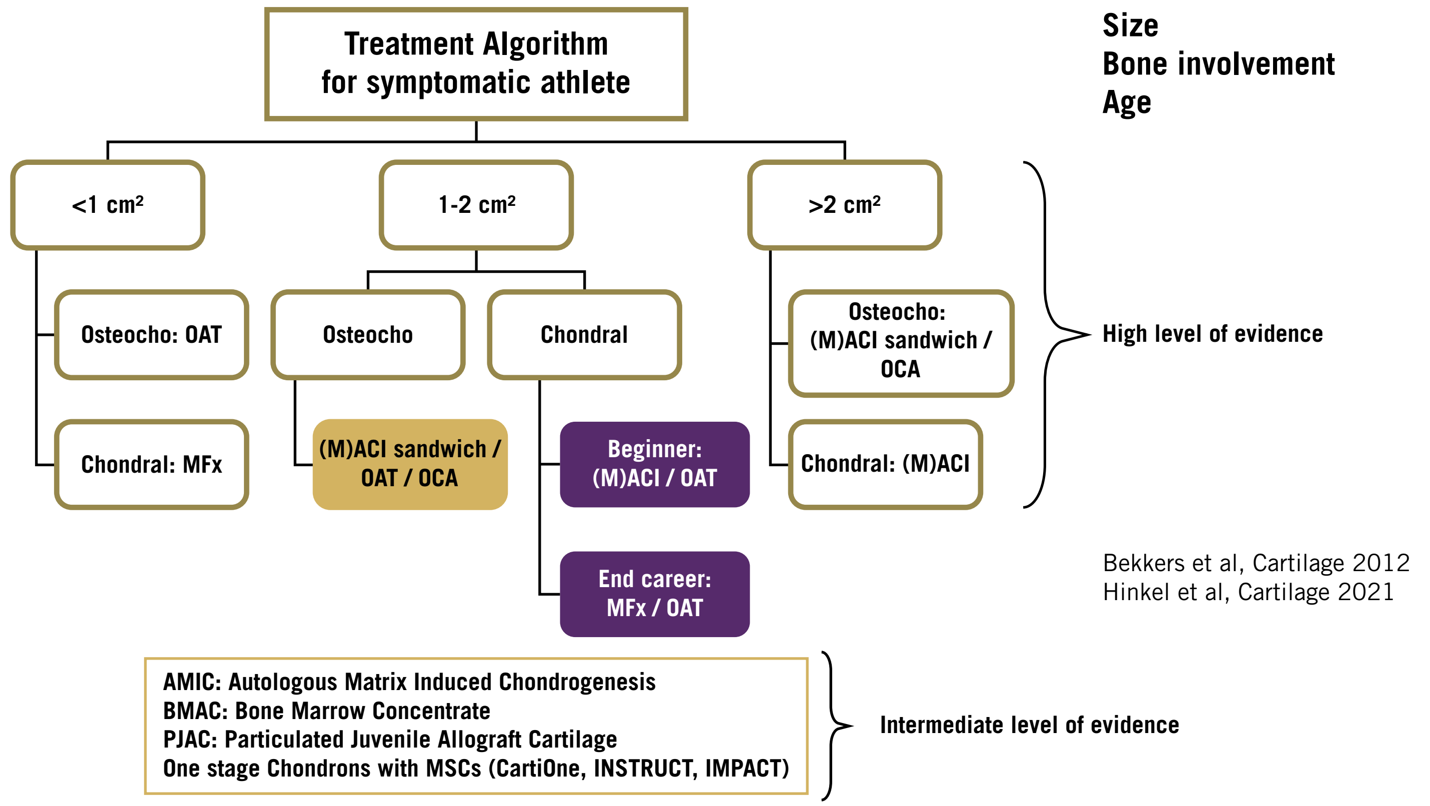

Figure 1: Treatment algorithm for sports cartilage injuries considering size, bone involvement and age. Suggestions from evidence.

Aa defect that is left untreated, or delayed (+1 year), or initially treated by means of bone marrow stimulation techniques, has shown the poorest of outcomes[14-17].

Predictors of a successful outcome are:

- Young patients with traumatic injuries (<25 yr in athletes, <30 yr in recreational athletes)
- Absence of delay in diagnosis and treatment (Within a year after the symptoms)
- Absence of previous surgeries or injuries
- Smaller mall defects (<2 cm²).

INDICATIONS FOR SURGERY

One of the challenges that the physician faces when dealing with an athlete suffering from a cartilage defect, is to determine whether the symptoms are correlated to the lesion. Many different parameters can play a role in the symptomatic condition of the athlete. Although cartilage defects are aneural, it is the pathophysiological lesion pathway that leads to pain and/or swelling. Therefore, conservative treatment, including physical therapy, medications, supplements, and intraarticular injections (Corticosteroids, HA, orthobiologics) are the first line approach and can assist the physician in the differential diagnosis.

This does not account however for defects with mechanical symptoms such as locking or catching. They often require a direct referral towards surgery.

Indications for surgery can be summarized by loss of function and/or disability, concomitant pathology, failure of nonsurgical treatment including intra-articular injections and clinical and/or radiological deterioration.

The most important parameter for the athlete is shown to be return to play. Any surgical shared decision making, or treatment algorithm will focus on this determinant factor[12]. Consequently, the timing and surgical treatment type are key factors to consider. Athletes with minor symptoms can sometimes try to delay treatment due to contractual or seasonal combined factors. However, once their performance is affected, the symptoms become more apparent or mechanical symptoms arise, surgery is indicated.

EVIDENCE-BASED TREATMENT ALGORITHM

The challenge remains to follow a common treatment algorithm for cartilage lesions in the athlete. The specific athletic needs and the multifactorial parameters require an individually tailored approach.

Predictive factors such as lesion characteristics, age and bony involvement are shown to be directly linked with early return to play and delayed rehabilitation timing[18,19,20].

CURRENT EVIDENCE

- Small defects do well with BMS or OATS (if one plug)[12,19] while AMIC and BMAC or One-Stage Chondrons and MSCs techniques are shown to improve outcome[21-25].
- Medium and large defects, (M)ACI and OATS or OCA provide longer durability and return to sport rates compared to BMS[26-37].
- When bone is involved OAT, OCA and (M)ACI (with Sandwich technique) yield better results .
- Return to sport rate ranges:(different indications as per the defect size)[11-12]:
  - OATS 89 – 93%,
  - OCA 88%,
  - ACI 82 – 84%,
  - BMS 58 – 75%.

FACTORS AFFECTING TREATMENT METHOD

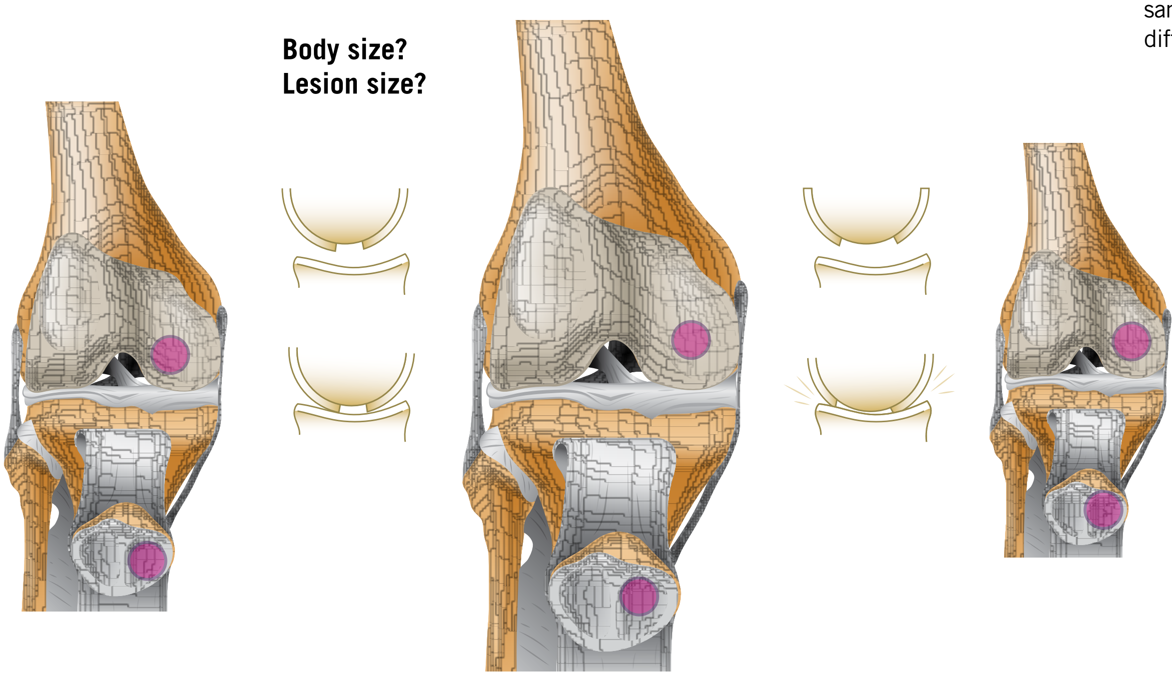

Figure 2: Size matters – same lesion dimensions in different sized knee joints.

The above presented research evidence justifies the treatment algorithm on surgical techniques according to the size of cartilage lesion, bone involvement and age of the athlete, as illustrated in Figure 1.

LESSONS LEARNED FROM SPORTS ENVIRONMENT REALITY

Debridement

Arthroscopic debridement is known to be a symptom-relieving technique with low morbidity, relative fast rehabilitation and return to play, low-cost with the disadvantage of providing only a short-term solution.

Especially in grade 2 lesions, good results can be obtained by debridement of the unstable cartilage fragments while creating smooth and stable defect edges[38]. Cartilage lesion debridement in the knee is shown to present with improved KOOS scores along the German Cartilage Registry, except for bigger lesions and combined partial meniscectomy[39].

The evidence on debridement indications are[40]:

- Partial thickness injury,
- Smaller lesions (2 to 3 cm²) in low demand individuals,
- Temporary solution during season competition
- Smaller lesions (2- 3 cm²) in late career athletes.

In a case series[41] on professional NFL players, the majority were able to return to play after chondroplasty - debridement for articular cartilage defects.

In a systematic review on RTP in football players who were treated by different surgical techniques, the authors reported a 100% return to play, approximately two and a half months postoperatively with evidence of fibrocartilage defect fill-up. However, 26% of the athletes developed additional cartilage lesions at a mean time of 1.6 years postoperatively, although in three out of four cases, the defect was found in another location[42,43].

Patients that were treated by a cartilage debridement, prior to a secondary ACI or Mosaicplasty procedure did not require the additional intervention in 27 % of cases[44].

Arthroscopic cartilage debridement (chondroplasty) is still a widely popular procedure[45-46] in sports surgery today ranging between 9 - 43%, with patellofemoral defects (49%) leading the indication as first line treatment[47,48].

Orthobiologics

The role of Orthobiologics in the treatment of athletic cartilage injuries can be summarized as follows:

1. Proof of safety in the use for cartilage injury and osteoarthritis

Current evidence provides the confirmation of safety with PRP and BMAC treatment options. Both look to cause minimal adverse effects (comparable or less) to similar injection therapies. Minor local inflammatory reaction with pain swelling or local skin reaction and low percentage of infection, bleeding or needle breakage are presented[49-53].

2. Clinical efficacy

Recent literature on intra-articular orthobiological injections presents with a reduction of symptoms without however any proof of tissue regeneration. These injections are considered symptom but not structure-modifying approaches. However, there is emerging evidence on the benefits of combining orthobiological treatments as adjunct to surgical cartilage repair[54-57].

3. Efforts to provide evidence

Although, Orthobiological injections are still considered unproven therapies for symptom modification in focal cartilage injuries of the knee, they can provide symptomatic relief in diagnosed Knee OA although its regenerative potential remains doubtful[58].

4. Non-Clinically driven decisions

In a survey among sports medicine physicians in the USA, orthobiological injections are used by a significant number of athlete doctors, with PRP being the most popular and OA being the predominant pathology to be treated. Additionally, reasons other than clinical efficacy (especially competitor utilization) were also identified as part of the decision making[59].

ONGOING DILEMMAS

Patient and lesion heterogenicity are commonly involved in the surgical decision-making process[12].

Several biases from the surgeon's perspective based on personal experience, familiarity with techniques and availability of technology need to be considered as well. Additionally, some remaining dilemma's need to be tackled further:

Size matters

A 2cm² MFC defect in a 1.65 m tall football player requires a different approach compared to a 2 cm² defect in 2.00 m tall Handball player (even in the exact same anatomic location) (Figure 2).

Site matters

A 2cm² lesion in the medial trochlea compared to a 2 cm² defect in the lateral trochlea, can result in a different symptomatology and impact on performance (Figure 3).

Bone involvement matters

A cartilage defect in the lateral femoral condyle of the knee (LFC) for example with: a) no bone edema, b) with bone edema, no tidemark abnormality, c) tidemark with waive appearance, and d) subchondral cyst, needs to be addressed in different ways.

Previous surgery complicates the decision-making process

Such as post-meniscectomy cartilage lesions.

Concomitant pathology needs to be addressed

ACL insufficiency, Trochlear dysplasia with patellar instability, Complex Lateral Meniscal tear, Varus alignment of the knee.

Timing is key

Early career stage athlete, long standing duration of symptoms (more than a year), unrealistic RTP expectations.

Seasonal challenges – Player role in the team

Differences in seasonal timeline, athlete level and individual expectations.

FACTORS AFFECTING TREATMENT METHOD

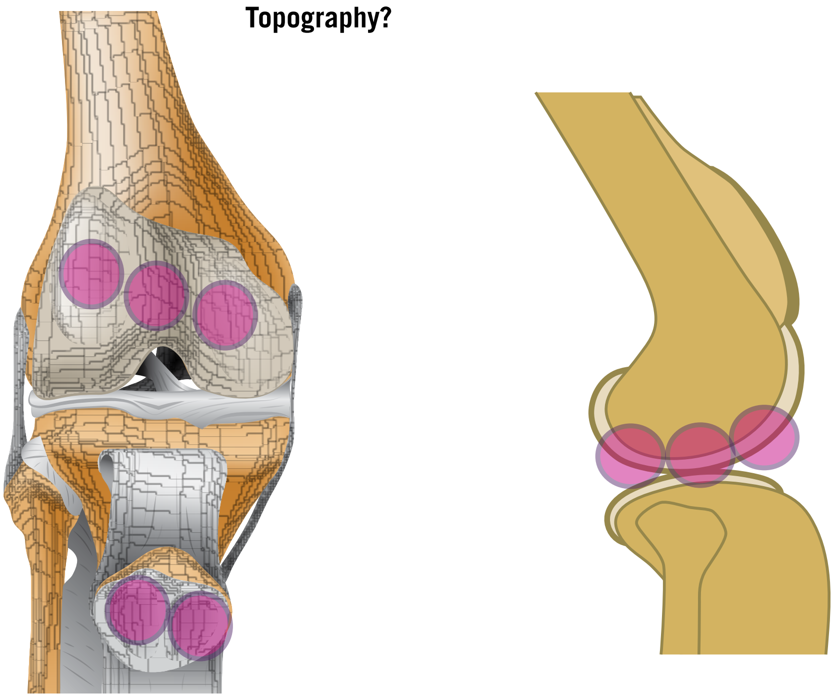

Figure 3: Site matters – same lesions in different anatomical site.

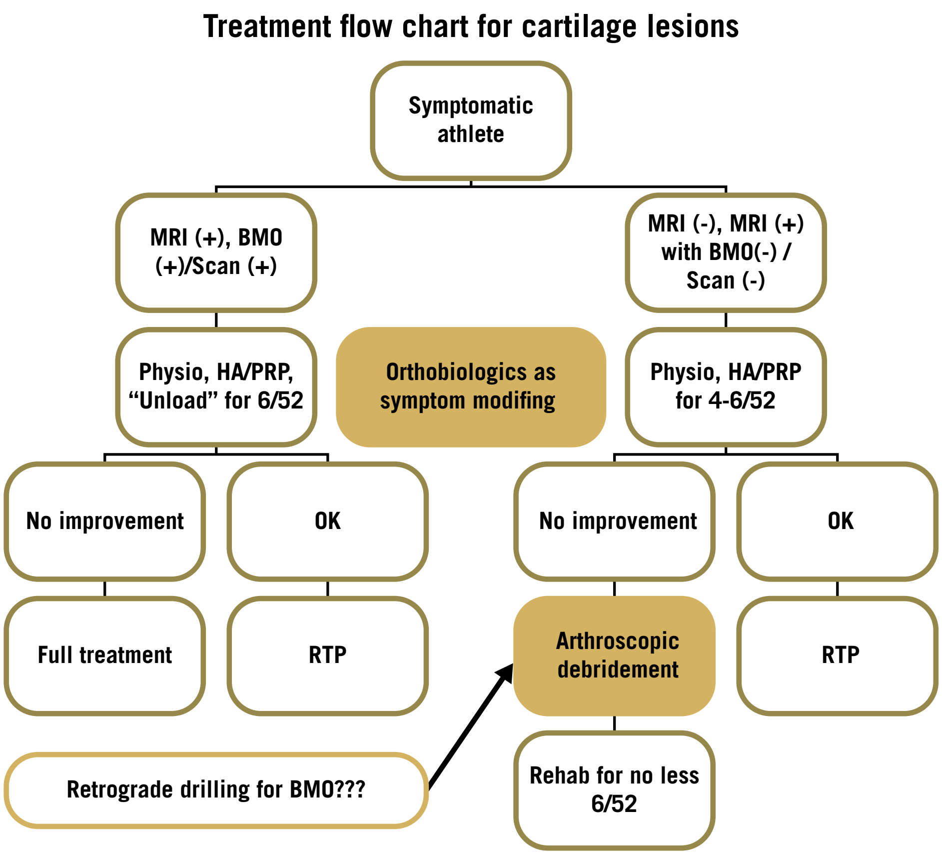

Figure 4: Treatment algorithm in symptomatic athlete - the Aspetar approach.

Image: Illustration.

All the above are daily examples of the challenges that a cartilage expert faces on a daily basis while dealing with athletes. Any surgical decision needs to be guided by scientific evidence and combined clinical expertise.

This shared decision-making process needs to remain centered towards the athlete – patient, while involving other stakeholders such as family members, agents, team officials etc. Realistic expectations need to be addressed after thorough expert evaluation together with provision of the scientific evidence as well as clinical experience and expertise.

Ultimately, any medical commitment to the athlete patient's condition goes all the way back to the ancient Greek Hippocratic oath «Ωφελεέειν, ή μη βλάπτειν», "First, do not harm".

The treatment of the symptomatic athlete with a cartilage defect is presented in the flowchart (Figure 4).

TAKE HOME MESSAGE

The treatment of cartilage lesions in the athlete remains a multi-factorial challenge despite a significant amount of new treatment options available.

An evidence-based history taking, clinical and radiological assessment and treatment algorithm allows the physician to indicate the correct and individualized athlete approach. Shared decision-making and realistic return to play protocols, tailored to the specific needs of the athlete are mandatory towards achieving the expected outcome.

References

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CARTILAGE RESTORATION SURGERY

WHAT IT TAKES TO MAKE IT A SUCCESS

– Written by Bashir Zikria, Qatar, Ali Noorzad, USA, and Zarko Vuckovic, Qatar

INTRODUCTION

Prior to the introduction of technological advancements in joint restoration and cartilage surgery, the operative interventions for patients with large cartilaginous and meniscal defects were limited. However, in recent years, surgical innovations in implants, technique, and biologics have provided surgeons with the tools needed to offer patients more options than were available in prior years. The surgical procedures are highly specialized and require a thorough understanding of the delicate relationship between biology, biomechanics, and surgical techniques of osteotomies, meniscal transplants, and ligament surgery. Our goal in this overview of articular cartilage restoration is to understand these delicate relationships and ultimately treat the patient successfully. A brief description of the various techniques and considerations utilized by successful joint restoration surgeons in managing these pathologies.

HISTORY OF CARTILAGE SURGERY

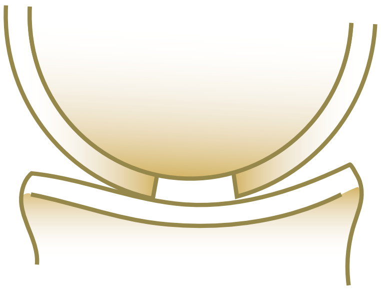
A brief history of joint restoration surgery is important to understand the progression from the first joint restoration procedure to the current state of joint restoration surgery. It's been almost a one hundred years that surgeons have recognized the importance of restoring the articular surface of the knee. The first knee cartilage restoration procedure was recorded by Lexer in 1925, when he reported the first osteoarticular transplant procedure[1]. Since then, further advancements have been made in osteochondral allograft transplantation by Drs. Gross, Meyers, and Convery[2,3,4,5] which was first used in tumor surgery. Bugbee introduced the procedure to sports medicine and has shown excellent clinical results in athletes. Marrow stimulation saw advancements from the classic Pridie method of the 1950s, which was an open method to stimulate regeneration of new collagen. This was then modified for arthroscopic procedures and initially began with "abrasionplasty" by Johnson, and marrow stimulation eventually evolved into the Steadman technique, which involved an arthroscopic debridement of the lesion and subchondral drilling to stimulate type 1 collagen formation[6]. We have now progressed to techniques in cell-based techniques for cartilage restoration. This first began with the work of Dr. Lars Peterson and autologous chondrocyte implantation in rabbit models in 1984[7]. Currently cellular therapy has progressed to third generation techniques.

MECHANISM OF CARTILAGE INJURY

A significant component of joint restoration procedures is a surgeon's thorough understanding of the knee as an organ. The ligaments, meniscus, and structures supporting the cartilage has to be optimum for the success of the surgery. Cartilage itself is a neural and avascular and depends significantly on the supporting structures. The anatomic and functional relationship between cartilage and the underlying subchondral bone is called the osteochondral unit. This basic unit is fundamentally important to understand when determining treatment strategies for joint restoration surgery. Basic science research has demonstrated that there is a very intimate relationship between articular cartilage and the subchondral bone where there is substantial crosstalk and cellular communication between these layers[8]. The cartilage layer is dependent upon oxygen and nutrient delivery from both the synovial fluid and the subchondral bone[9,10].

The articular cartilage provides a layer of protection to the underlying subchondral

1a **SMALL LESION < 2CM^2**



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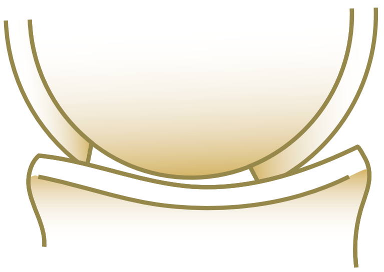

Figure 1: (a and b) Symptoms of small vs large lesion. "Feeling of instability".

Figure 2: Long leg films to determine Mechanical Axis: the line drawn from the center of the femoral head to the center of the ankle. This line should be in approximately in the center of the knee.

bone and provides a low-friction gliding surface, while also distributing joint load over a wide area, and thus minimizing peak pressures upon the subchondral bone[11,12]. What we do know if the osteochondral unit is maintained and there is no significant injury, the cartilage can be functional for a lifetime. Ponzio et al demonstrated that marathon runners, range up to 79 years old had a lower degenerative change in their knee than the general population[40]. Despite receiving nutrients and oxygen from both the synovial fluid as well as the underlying subchondral surface, the articular cartilage unfortunately has very poor healing potential following injury. We also know that the environment or synovial milieu of the knee must be healthy to support the cartilage of the knee, because a constant inflammatory environment will eventually break down the cartilage. The chondral injury can lead to changes in the subchondral bone, and this can play an important role in the development of osteoarthritis. The natural history of these injuries can progress and gradually lead to osteoarthritis, which can cause a tremendous burden on health care systems[41].

Chondral injuries are common and arthroscopic studies have demonstrated up to 60 chondral injuries at the time of arthroscopy and up to 10 percent full thickness lesions. In ACL injuries, up to 60 percent of the chondral lesions may be full thickness. Most of these lesions are asymptomatic and depending on size, location, and depth can become symptomatic over time. Patients who have sustained an articular cartilage injury typically present with pain, swelling, mechanical symptoms, instability, and often report a history of trauma. Any patient with recurrent pain and swelling should have chondral injury on their differential diagnosis. A focused clinical exam on the extremity of interest will often times demonstrates an effusion, pain with active and passive range of motion, and joint line tenderness. The instability that patients feel is not necessarily to an unstable knee but whenever the defect is loaded, there is a feeling of "giving out" or falling into the defect. The larger the defect the more the feeling of instability (Figure 1). Careful inspection of the skin and soft tissue should be completed to evaluate for muscular atrophy and prior incisions. The joint of interest should be evaluated with provocative tests to evaluate the integrity of cruciate and collateral ligaments. A clinical observation with the patient standing and walking can provide valuable information regarding gait antalgia and biomechanical limb malalignment.

Radiographic evaluation typically consists of plain radiographs, standing long leg views for assessment of mechanical alignment, and magnetic resonance imaging. Ideally, an experienced musculoskeletal radiologist is available to assist in evaluating MRI images for ligamentous injuries, meniscal pathology, and lesions of the articular cartilage (Figure 2). In the presence of an articular cartilage injury, there are scoring systems that MSK radiologists use for grading cartilage injuries and repair procedures. The Mocart (Magnetic Resonance Observation of Cartilage Repair Tissue) and AMADEUS (Area Measurement And Depth Underlying Structures) scores are typically calculated to evaluate and grade osteochondral lesions pre- and post-surgery to determine the quality of the chondral repair[13].

TREATMENT

The overall goal of non-operative management in articular cartilage injuries is to improve pain, improve function, and to delay surgery for as long as possible[14]. In the non-operative management of these conditions, AAOS guidelines have provided strong recommendations for physical therapy and NSAID usage and only moderate recommendations for utilization of brace and BMI control; additionally, diagnostic arthroscopy is not recommended.

Surgical options can be discussed once non-operative management options have been exhausted or if the patient has been experiencing unacceptable pain and dysfunction. Once surgical candidacy has been determined, a surgeon must consider the contributing variables to the patient's pathology such as ligamentous insufficiency, meniscal pathology, and structural malalignment. These comorbid conditions can change the knee joint biomechanics by overload of a compartment, instability, and finally a direct injury can lead to further breakdown of the knee. These surgeries are complex because the patient may need on occasion several procedures and may even have to be staged. Prior to scheduling the patient for surgery, they must be made aware of the recovery process, demonstrate a willingness to participate in post-operative rehabilitation protocol, and have clear expectations regarding their prognosis.

Once a patient's surgical candidacy has been determined, the primary surgical treatment of choice is dependent on the size, depth, and location of the osteochondral lesion, as well as the patient's overall level of function, activity, and the age of the patient. Another key factor is the patient's expectations, and the surgery should match their expectations or the patient will be disappointed even though the surgeon himself thought the surgery was a success. The integrity of the underlying subchondral bone must be evaluated for presence or absence of subchondral edema, cystic changes, or any evidence of bony bed compromise. Based off of these factors, the primary surgical intervention to address their cartilaginous lesion may be a simple debridement (chondroplasty), a microfracture procedure, an osteochondral autograft or autograft transplantation, or cellular techniques such as matrix associated autologous chondrocyte implantation (MACI). Secondary surgical interventions must address underlying conditions that may have predisposed the patient to a cartilaginous injury such as ligamentous instability, bony malalignment, or meniscal deficiency. These may be addressed with ACL or any instability repair or reconstruction, realigning osteotomies, and meniscal repairs versus transplants, respectively. The successful joint restoration surgeon has to be comfortable with performing all of these procedures since up to 50% of restoration surgery will involve a concomitant procedure to address the underlying comorbidity along with the chondral procedure.

There are several algorithms for cartilage restoration (Figure 3). These are usually based on size, location, depth, and activity level. While there might be slight differences to which procedure is best for the chondral repair, addressing the comorbidities are the same in all algorithms. It is essential to be comfortable with these procedures or the final cartilage restoration procedure will be more likely to fail. Bode et al demonstrated that MACI success dropped in patients without addressing their malalignment from 89% survival to 58% survival[42]. To preserve any osteochondral procedures, it is imperative to scrutinize the native mechanical alignment, evaluate the joint surface, and perform the appropriate osteotomy for the respective deformity[15]. Common osteotomies include high tibial osteotomy for the varus knee, distal femoral osteotomy for the valgus knee, and tibial tubercle osteotomy for patellar instability or patellofemoral pathology[16,17]. These procedures are indicated to provide for more symmetric joint surface loading; however, they are to be avoided in patients with

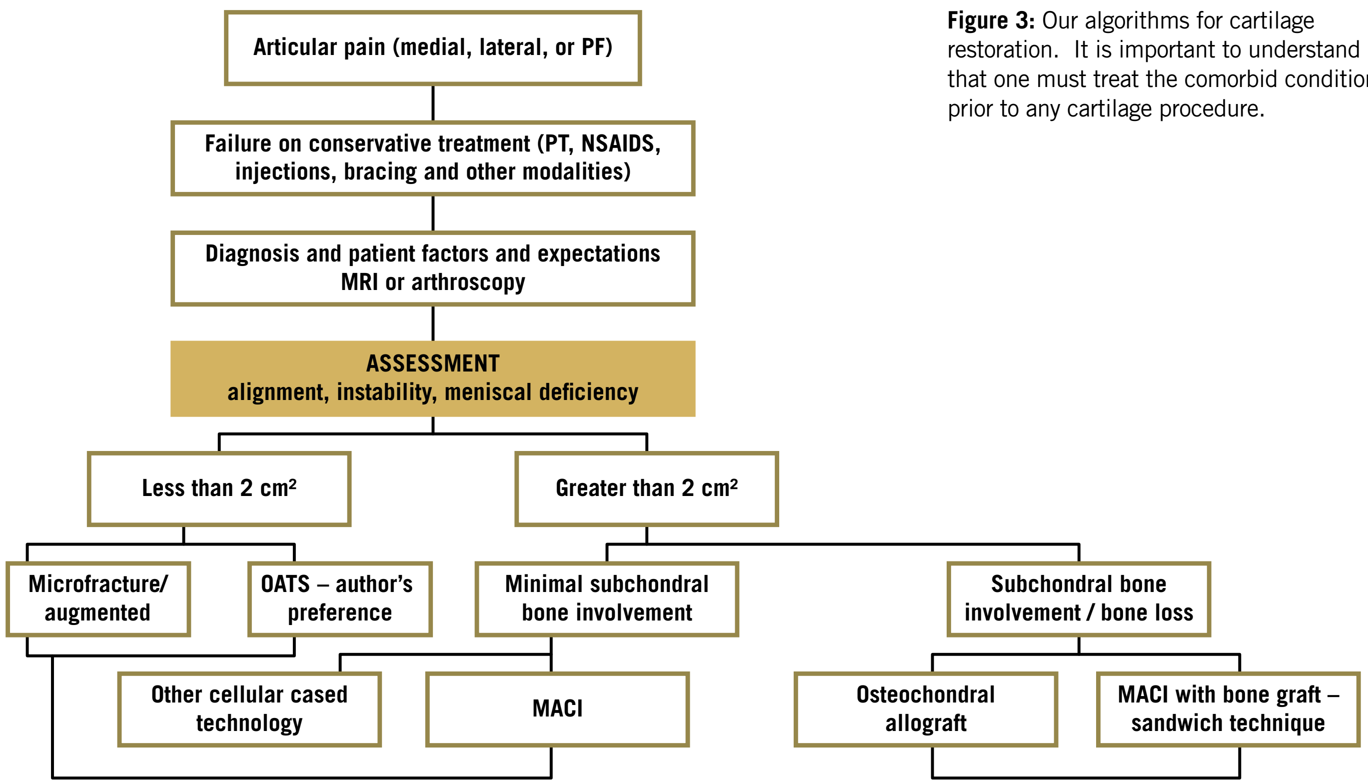

Figure 3: Our algorithms for cartilage restoration. It is important to understand that one must treat the comorbid conditions prior to any cartilage procedure.

inflammatory arthritis and those who are current smokers[18,19].

The high tibial osteotomy can be utilized to correct deformities in both the coronal and sagittal planes and can be completed with a closing wedge or opening wedge osteotomy. While the closing wedge osteotomy was once the most commonly used technique, opening wedge osteotomies have become the more preferred option given their perceived greater safety, relatively less challenging surgical technique, as well as the ability to fine-tune the correction after the osteotomy has been performed[20] (Figure 4). Additionally, medial opening wedge osteotomies offer a low risk of injury to the common peroneal nerve while also avoiding any violation of the posterolateral structures and tibiofibular joints. However, unlike a closing wedge osteotomy, the opening wedge relies on a bone graft to maintain the correction which inevitably increases risk of delayed healing, nonunion, possible loss of correction, and extended weight-bearing restrictions[21]. Lateral closing wedge osteotomies on the other hand, do not rely on bone grafts and are permitted earlier weight-bearing, however if the lateral approach requires a fibular osteotomy, then there is also a risk of peroneal nerve injury and fibular nonunion[22].

In patients with genu valgum deformity, the distal femoral osteotomy is another tool utilized by joint restoration surgeons. Medial closing wedge osteotomy and lateral opening wedge osteotomies are two techniques to produce a neutral mechanical alignment[23]. Distal femoral osteotomies are less commonly utilized than HTO's, comprising approximately 5-10% of corrective osteotomies.

In patients with patellofemoral pathology, a tibial tubercle osteotomy may be utilized for the appropriate pathology. An osteotomy of the tibial tubercle can be mobilized and placed in position of stability given the specific etiology. For patients with patellofemoral pathology and patella alta, a TTO may be performed, and the tibial tubercle can be anterior, anteromedial, distal, or proximal[24,25].

As previously mentioned, the goal of corrective osteotomies is to minimize pain, disability, and delay arthroplasty for as long as possible. Several studies have demonstrated reassuring outcomes up to a decade past surgery. Pincewski et al reported 79% survival at 10 years, with 85% of patients satisfied with their result at 12 years[26]. In a meta-analysis performed by Lee et al, investigators found 91% survival at 10 years in patients who had undergone a medial opening wedge high tibial osteotomy[27].

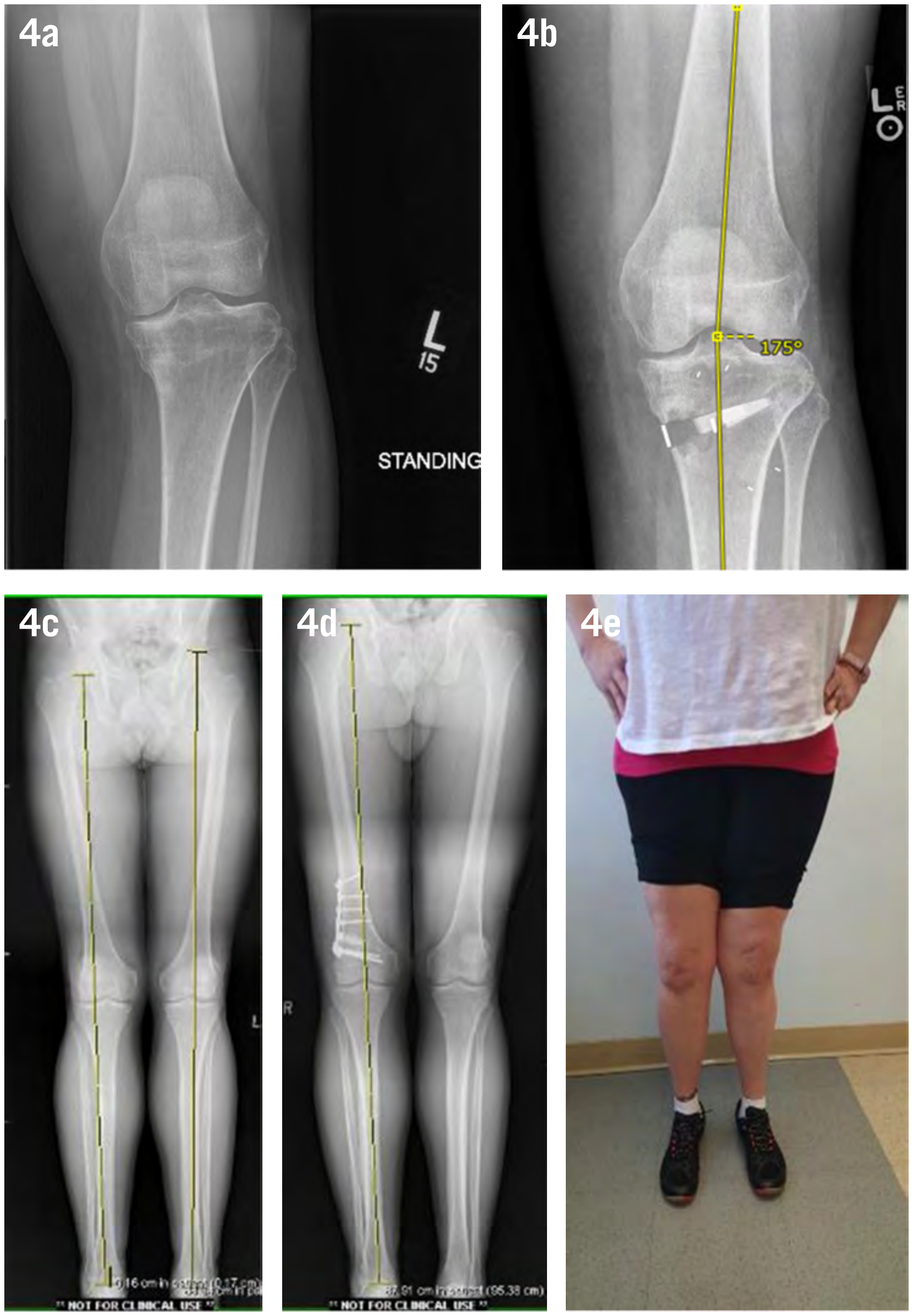

Figure 4: (a and b) High Tibial Osteotomy. (c, d, e) Right knee distal femoral osteotomy.

Despite these reassuring outcomes, corrective osteotomies do carry their own risk of complications. Complications that surgeons must be cognizant of include but are not limited to fracture, failure of fixation, and infection. Additionally, there is the risk of over or under correction, delayed union/non-union, and risk of neurovascular injury[19].

Corrective osteotomies are recommended in the appropriate patient population as they can help preserve the quality and the longevity of a concomitant cartilage procedure. In addition to osteotomies, meniscal procedures must also be considered to preserve cartilage restoration surgeries[28]. Patients that require a cartilage procedure must also have a functional meniscus. In patients who have undergone a subtotal or total meniscectomy,

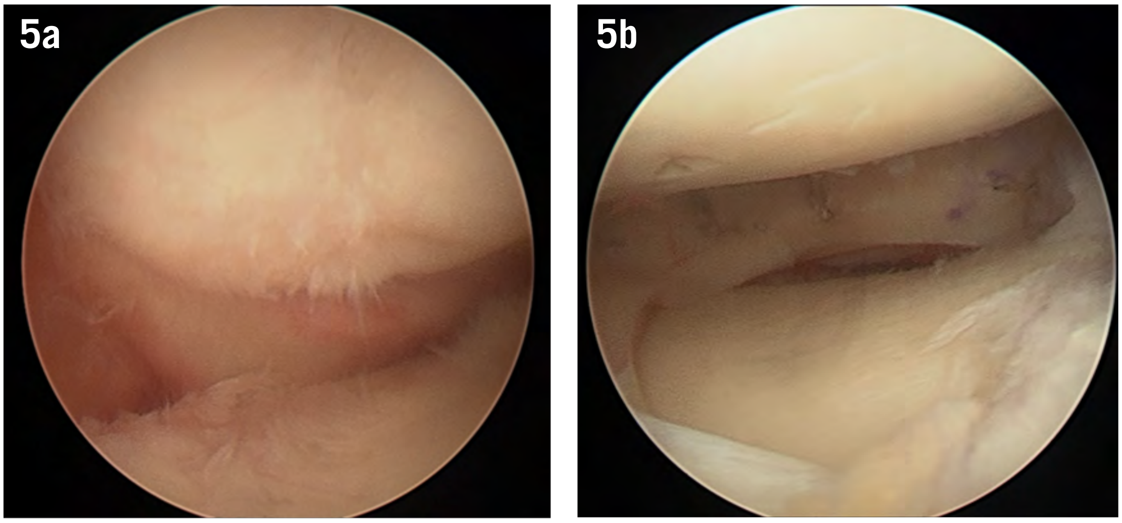

Figure 5: Meniscal transplantation (lateral meniscus).

Figure 6: Microfracture and oats procedures.

a meniscal transplant should be considered prior to any osteochondral procedure[29,30] (Figure 5). Preoperative planning for this type of procedure typically consists of AP and lateral imaging, and using the Pollard technique, radiographic measurements are acquired on AP and lateral views[31]. Non-irradiated fresh frozen or viable meniscal allografts are prepared for transplant and secured to the tibial plateau through slot or bone plug techniques[32]. In a meta-analysis by Verdonk et al, meniscal transplant was deemed a viable option only in young patients and found 80% survival rate at about 5 years[33]. Samitier et al reported a 75% return to sport rate, and a failure rate of about 10-29%[34].

The role of corrective osteotomies and meniscal transplants in cartilage surgery is to provide the optimal environment for the respective osteochondral procedure. Also, any ligamentous instability, such as ACL or multiligament injury, must be addressed at the time of surgery. The instability will likely cause failure of the cartilage restoration procedure. The most common treatments performed for chondral injury are chondroplasty and microfracture. The main reason is these procedures are inexpensive and technically less challenging than the other procedures. Most surgeons have learned these procedures during their residency and fellowships. Generally, we reserve these procedures for small lesions less than 1 cm and in areas where there is not much loading. The goal of microfracture is to drill into the subchondral bone and release mesenchymal stem cells that fill the lesion with fibrocartilage or type 1 collagen, Bone marrow stimulation technique (Figure 6). We rarely do microfracture in our practice because most of the smaller lesions are asymptomatic and we treat conservatively. There has been advancement in the technique of microfracture in recent years by adding a scaffold to create an enhanced chondrogenic environment[43]. We only treat symptomatic patients who generally have larger lesions in loading areas of the knee. Small lesions in areas of high load, we treat with osteochondral autografts (OATS). The OATS procedure is transferring healthy cartilage from a non-weight bearing of the knee to a chondral defect in the weight bearing area of the knee. The OATS is limited by donor availability and limited to smaller lesions. Studies demonstrate that the OATS procedure is superior to a microfracture technique in the treatment of smaller load bearing defects[44]. In our practice and most of our patients have moderate to large lesions generally over 2 cm^2. Osteochondral allografts are the treatment of choice for patients with significant damage to the osteochondral unit and injury that results in significant subchondral bone loss or subchondral changes. Utilization of an osteochondral allograft for a large cartilage lesion is considered a salvage procedure. Studies have shown a graft survival rate of 79% at 10 years, and 73% at 15 years[35] (Figure 7).

Our preference for large lesions without significant bony involvement is a cellular based repair technique such as the MACI. Matrix-associated chondrocyte implantation procedures should be considered in patients between ages 15-55 with large, full-thickness defects that less than 6 mm in depth. Despite the disadvantages of being a staged procedure

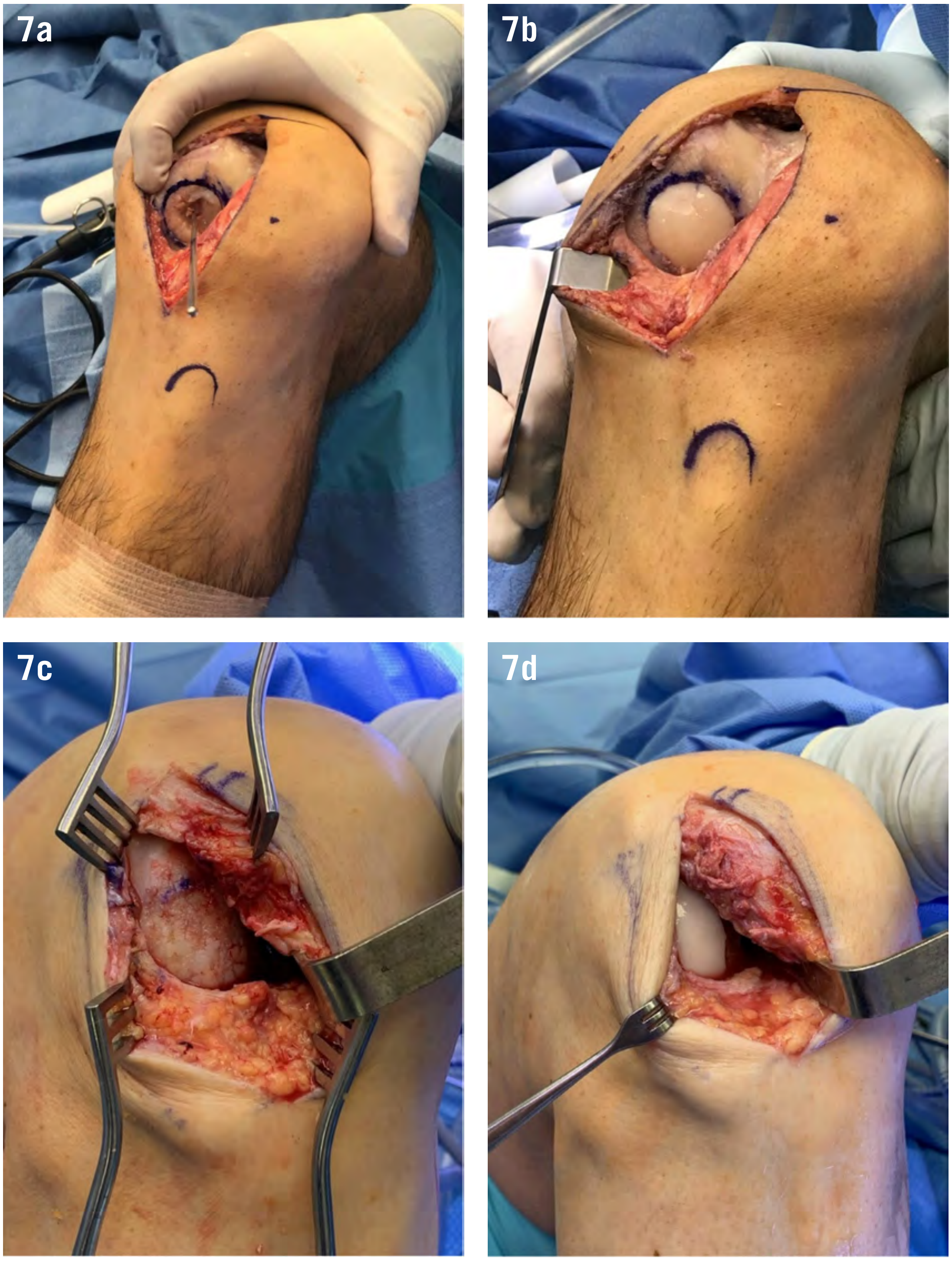

Figure 7: (a and b) Osteochondral allograft. (c and d) Osteochondral allograft – biological unicondylar allograft.

and added cost, the technique is bone preserving and allows the ability to treat lesions of a variety of sizes, shapes, and locations[36]. Since the first generation of autologous chondrocyte implantation techniques of the late 1990s, there have been significant technical advancements in this procedure. Modern day third generation techniques allow efficient, uniform distribution of cell density across the ACI membrane, while also providing an improved delivery mechanism to allow even delivery of the chondrocytes to the defect[37]. Several level 1 and 2 studies have demonstrated improved long-term outcomes in patients with MACI procedures over those with microfracture[38,39] (Figure 8).

CONCLUSION

In conclusion, joint restoration surgery is challenging and should be delayed and deferred for as long as possible through activity modification, weight loss, and physical therapy. When non-surgical options have been exhausted, the treating physician should have a thorough understanding of the intimate relationship between biology, biomechanics, and the technical ability to identify and correct the respective pathology. Corrective osteotomies, ligamentous repairs, and meniscal transplants are the variables that promote longevity in concomitant osteochondral procedures.

8a

8b

Figure 8: MACI procedure.

Appendix I: KEY FACTORS TO SUCCESS

1. *Patient Factors: Age, activities, and expectations*
   - *a. Rehab potential*

2. *Lesion Factors:*
   - *a. Location: - weight bearing area and patellofemoral joint*
   - *b. Size: Greater than 2cm²*
     - *i. Smaller lesions: possibly asymptomatic*
   - *c. Depth: amount of bone involvement*

3. *Comorbidities: Surgeon must be comfortable with these PROCEDURES:*
   - *a. Alignment*
     - *i. Osteotomies*
   - *b. Instability*
     - *i. ACL*
     - *ii. Multiligament injuries*
   - *c. Meniscal pathology*
     - *i. Meniscal transplantation*
4. *Cartilage technique*
   - *a. Bone marrow stimulation: smaller and possible with scaffold*
   - *b. Osteochondral autograft vs. allograft*
     - *i. Choice depends on size of lesion and availability of donor site*
   - *c. Cellular based technique*
     - *i. MACI*
       - *1. 2 stages*
       - *2. Workhorse for PFJ*

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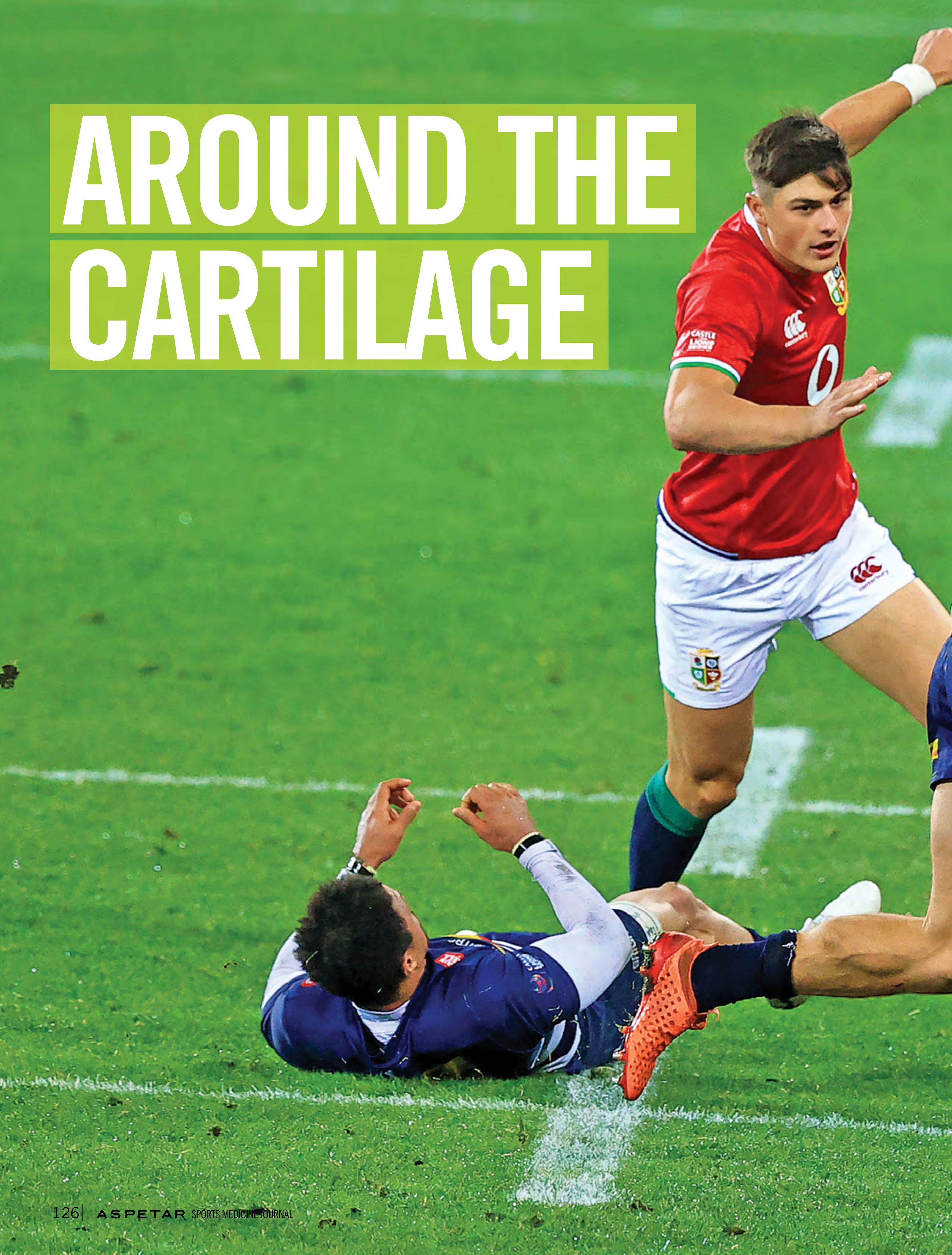
AROUND THE CARTILAGE



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OSTEOCHONDRITIS DISSECANS OF THE KNEE

CONQUERING A CHALLENGING ENEMY

– Written by Theodorakys Marín Fermín, Venezuela, Bruno Olory, and Khalid Al-Khelaifi, Qatar

INTRODUCTION

Epidemiology and Clinical Presentation

Osteochondritis dissecans (OCD) is an osteochondral unit disease characterized by the sequestration of subchondral bone and subsequent delamination and instability of the overlying cartilage[1-3]. König was the first to coin the term in 1888 and it has become an increasing cause of knee pain among young patients, with a prevalence of 15-29 per 100,000 population[4,5]. The most commonly affected location is the lateral surface of the medial femoral condyle, followed by the lateral femoral condyle and the patella[6].

OCD diagnosis is more frequent during the second decade of life, as an incidental finding or presenting symptoms during physical activity[1]. It can be categorized as juvenile and adult OCD[7]. Symptoms include pain, joint effusion, locking or catching, and functional impairment, which can be as severe as those presenting patients waiting for a knee replacement[2,8].

Pathogenesis and Natural History

OCD pathogenesis is not entirely understood. Several factors, including biological and mechanical, have been suggested to participate in its development. Genetics, ossification center deficit, endocrine disorders, tibial spine impingement, discoid meniscus, injuries, and overuse remain under discussion as causative factors[1].

The typical evolution of the resulting osteochondral lesion is the natural filling of the defect bed with fibrocartilage, a form of cartilage constituted by collagen type I fibers. However, fibrocartilage mechanical properties lack those of hyaline cartilage[2,9]. Thus, the aim of any treatment in the management of OCD is to preserve a congruent joint with hyaline cartilage and correct alignment to avoid the progression to osteoarthritis[2]. Therefore, successful long-term treatment outcomes of this condition are of paramount importance, considering that OCD predominantly affects children and adolescents[10-12].

DIAGNOSTIC IMAGING

Plain radiographs and magnetic resonance imaging (MRI) studies are essential in diagnosing OCD (Figures 1 and 2), which can be bilateral in 15% of the patients. Anteroposterior, lateral, tunnel, and skyline views compose the battery for examination, the latter when patella involvement is suspected[6].

MRI is the definitive imaging study, as it provides the most information about the lesion, including size, volume, presence of loose bodies, and confirming radiographs findings (Figure 3). The fragment appears as a hypointense image in T1, usually extending to the trochlear notch when affecting the medial femoral condyle, with underlying bone edema. Other findings include a subchondral bone puzzle configuration and spicules corresponding to secondary ossification centers[6].

Furthermore, T2-weighted images are valuable in assessing fragment stability with high sensitivity and specificity in adults[13]. High-signal-intensity rim at the interface and extending through the articular cartilage, fluid-filled cysts underneath the lesion, and a focal defect filled with joint fluid are typical of unstable fragments[13,14].

Additionally, in juvenile OCD, it is reliable assessing the following signs when suspect fragment instability: interface rim with the same signal intensity as joint fluid, a second outer rim of T2-weighted low-signal intensity, or multiple breaks in the subchondral bone plate on T2-weighted MRI[13,15].

CONSERVATIVE MANAGEMENT: THE FIRST-LINE TREATMENT OF STABLE LESIONS

Conservative management remains the first-line treatment for small and stable lesions in young patients. Patient education about disease behavior is of paramount importance, and counseling on the importance of restricting sporting activities[16].

Conservative treatment traditionally consists of activity restriction with or without weight-bearing or immobilization, therapeutic strengthening exercises, and modalities such as external shockwave therapy[16]. A systematic review by Andriolo et al[16] revealed an overall healing rate of 61.4% in patients undergoing conservative treatment. However, high variability among the included studies was noted. They also identified several risk factors that potentially contraindicate conservative treatment, like larger lesion size, more severe stages, skeletal maturity, and older age, as well as the presence of joint effusion or locking. Moreover, according to their findings, the only restriction of sports and strenuous activities seems advantageous over further limitations.

It is advisable to limit running, jumping, squatting, or activities with repetitive and compressive stress on the affected knee until symptoms relief and imaging alterations show healing progress[16].

SURGICAL TREATMENT OPTIONS: AN INSIGHT TO THE ARMAMENTARIUM

Surgical treatment is the preferred approach for symptomatic lesions presenting with joint effusion and locking or catching of the knee[2]. The size and depth of the lesion, patient's age, activity level, and the presence of degenerative changes play a vital role in the decision-making[2,17].

Figure 1: AP X-ray of the knee a skeletally immature patient with a displaced osteochondritis dissecans lesion on the lateral femoral condyle.

Figure 2: AP X-ray of a typical lesion of osteochondritis dissecans in a teenager with closed physis on the medial femoral condyle.

Figure 3: Magnetic resonance imaging sagittal view of a patient with a big and unstable osteochondritis dissecans lesion.

Also, lesions with a higher odd for developing osteoarthritis should be considered individually[10]. The risk is notably higher in those lesions where incongruity is present, such as type III and IV lesions, according to the International Cartilage Regeneration and Joint Preservation Society (ICRS) (Table 1)[2,18].

Surgical Procedures

Drilling

Drilling is advisable for stable lesions that failed conservative treatment and OCD ICRS grade I and II lesions[19]. This procedure aims to create bone channels that allow healing of the osteochondral unit above it[6]. There are two techniques, trans-articular and retro-articular drilling. Both methods are satisfactory and have shown good results[20,21]. Kirschner wires can be used for this purpose (Figure 4), with a suggested depth ranging from 18 to 20 mm, if trans-articular. Fluoroscopic control during the procedure is recommended in skeletally immature patients. Postoperatively, non-weight bearing is advisable for 4 to 6 weeks and should be followed by plain radiographs. With proper rehabilitation, patients can go back to normal sports activities within 4 to 6 months post-operatively[6].

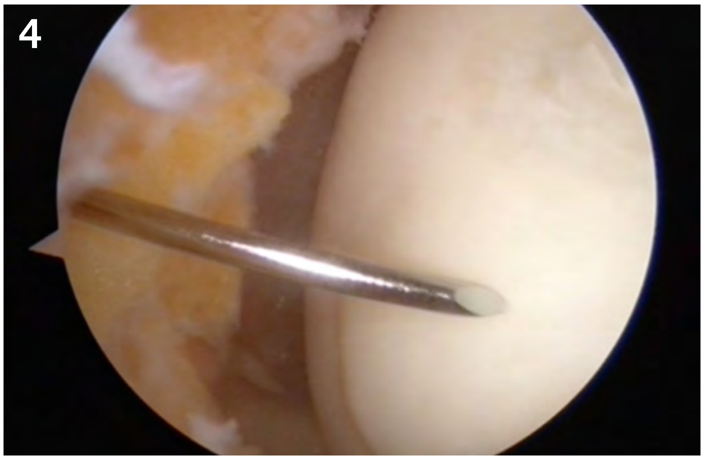
Fragment Fixation

Fixation is the first surgical option for osteochondral fragments that are unstable or loose[6]. It has the potential to restore the native cartilage surface and can be performed open or arthroscopically with stimulation of the defect bed[2]. After assessing the stability of the lesion and confirming its instability, it is critical to debride the subchondral bone underneath the fragment (Figure 5). Moreover, if the

TABLE 1

Grade	*Description*
I	*Stable lesions with a continuous but softened area covered by intact cartilage.*
II	*Lesions with partial discontinuity that are stable when probed.*
III	*Lesions with a complete discontinuity that are not yet dislocated ("dead in situ").*
IV	*Empty defects as well as defects with a dislocated fragment or a loose fragment within the bed.*

Table 1: The International Cartilage Regeneration and Joint Preservation Society osteochondritis dissecans lesion classification[18].



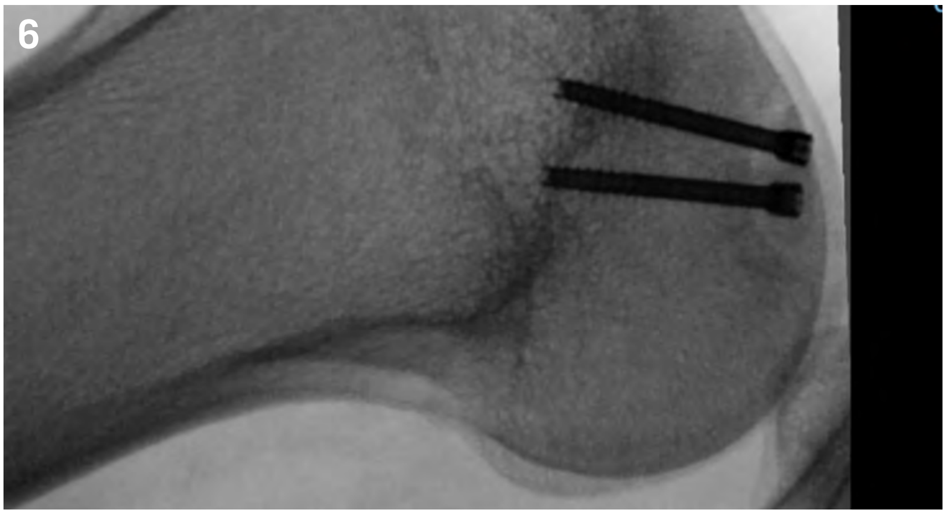


Figure 4: Trans-articular drilling of a stable lesion after careful arthroscopic examination and assessment of the stability of the diseased osteochondral unit.

Figure 5: Arthroscopic examination of ICRS grade III lesion and introducing a shaver just below the diseased osteochondral unit to debride the fibrous tissue until bleeding bone.

Figure 6: Intra-operative fluoroscopy showing the fixation of the fragment with two metallic headless screws.

subchondral bone is scarce, it is essential to bone graft the void previous to reduction and fixation of the lesion[6].

There are several available implants for this purpose, including headless screws, bioabsorbable pins, or nails[2]. Osteochondral autograft plugs harvested from non-weight bearing areas are also among the options to fix the unstable fragment. Several studies have shown the benefit of bioabsorbable and metallic screws (Figure 6)[22,23]. Among the advantages of bioabsorbable screws is that the patient does not need further surgery for hardware removal. Correspondingly, the metallic headless screws allow a better and rigid fixation for the fragment, leading to a higher healing rate (Figures 7 to 10). The patient post-operatively will be non-weight bearing for two months, and if the osteochondral fragment was fixed with a metallic screw, the patient is expected to need another surgery for its removal[6].

According to a systematic review by Leland et al[24], the rate of radiographic healing after fixation in adult OCD ranges from 67%-100%, with satisfactory improvements in Lysholm and IKDC scores. Although, the quality of literature addressing the fragment healing ability in skeletally mature patients remains scarce.

Reoperations are common complications, accounting for up to 44% of loose body removal. Chondral revision and unplanned removal of hardware are also common causes for reoperations[2].

Restorative Procedures

Restorative procedures are indicated when the reparative procedures fail or if the osteochondral unit is not repairable from the start. They depend on the size and location of the diseased cartilage.

Osteochondral Autograft Transplant (OAT) and Mosaicplasty

In OAT, a mature hyaline cartilage local graft is harvested from a non-weight bearing area of the knee and transplanted, providing immediate coverage of the defect area open or arthroscopically. Similarly, in mosaicplasty, many smaller osteochondral grafts are transplanted to fill a cartilage defect[25].

Both techniques have been widely studied and implemented, yielding satisfactory results, especially for OAT. However, as mosaicplasty has been used to treat larger defects, both are not amenable for comparison[26]. It is essential to point out that the reproduction of curved cartilage areas can be challenging, and thus, such procedures should be done by experienced surgeons[27]. Additionally, concerns exist regarding mosaicplasty as the spaces between graft plugs are filled with fibrocartilage[28].

Medium- and long-term results are satisfactory, particularly when patient selection is driven appropriately[2]. Active young males (< 40 years old) with cartilage defects < 3cm² have shown to have the best outcomes[29].

Autologous Matrix-Induced Chondrogenesis (AMIC)

AMIC is a bone marrow-stimulation augmentation procedure in which a scaffold concentrates and distributes the migrating cells, improving the healing of the cartilage defect[2,6]. Randomized controlled trials have demonstrated AMIC to have similar clinical results as bone marrow stimulation alone at a year. However, AMIC results are maintained up to 5-year follow-up with a superior filling of the defect and quantity of hyaline cartilage and only 7% failure compared to 66% in the microfracture group[30,31].

Scaffold versatility lies in the possibility to treat lesions with different sizes and shapes and the lack of need for highly specialized laboratory settings, standing out as a single-stage procedure[2]. Furthermore, newer techniques remove the need to violate the subchondral bone in the form of bone marrow aspirate concentrate[32].

Autologous Chondrocyte Implantation (ACI) and Matrix-Assisted Autologous Chondrocyte Implantation (MACI)

ACI has shown good clinical results and better durability when compared to microfractures[17]. It is a two-stage procedure in which chondrocytes are harvested from a local non-weight bearing zone of the knee and cultured in highly specialized laboratories for a second procedure involving its implantation in the lesion site with or without a scaffold[17].

> ***Conservative management remains the first-line treatment for small and stable lesions.***

The characteristics of the new cartilage have been reported to be better than those observed in other bone marrow stimulation procedures[33]. Techniques involving chondrocyte implantation are the preferred method of choice in treating ICRS grade IV full-thickness cartilage injuries and those involving subchondral bone. The latter may benefit from bone grafting and double-layer implementation, the so-called sandwich technique[34].

In a systematic review by Sacolick et al[17] comprising nine studies, they found that patient-reported outcomes after ACI in OCD were significantly better, with negligible complication and failure rates. The lesion size and age of the patient revealed contrasting differences. Outcomes were better in the young population undergoing surgery, contrasting to adults, where surgery was the preferred approach with less satisfactory results.

Costs of restorative procedures are still their main limitation; despite the gathered evidence, its widespread implementation has not been feasible[35-37]. Nevertheless, technical developments have allowed

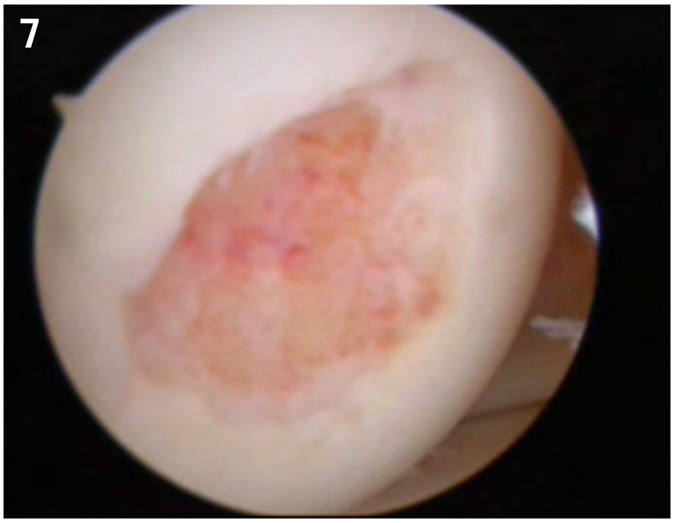


Figure 7: Intra-operative arthroscopic view of a full-thickness lesion at the femoral condyle.

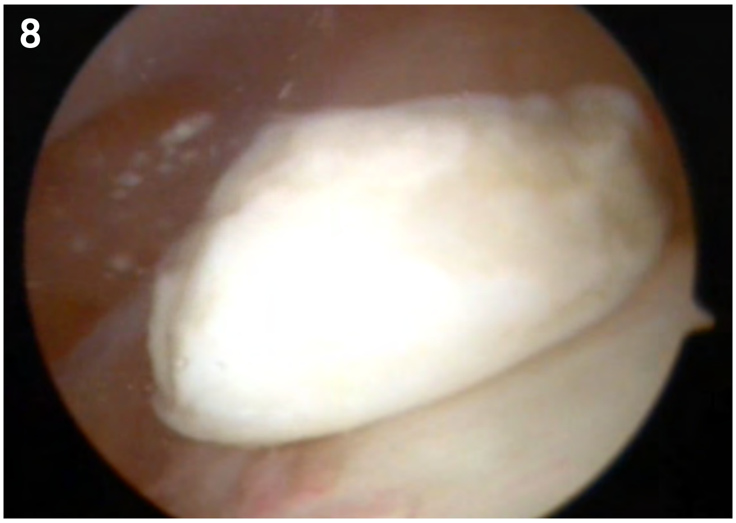


Figure 8: Intra-operative arthroscopic picture showing the detached fragment.

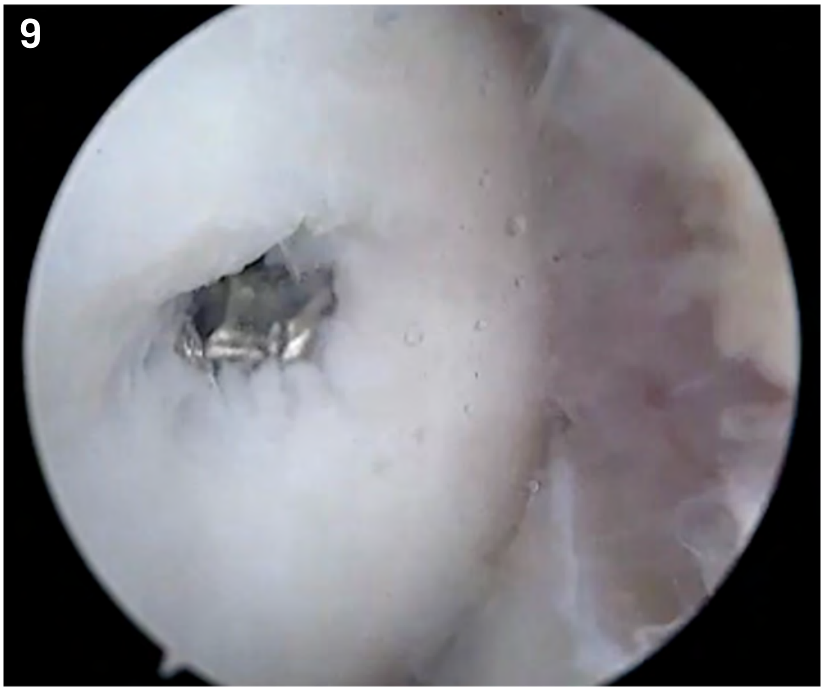


Figure 9: Intra-operative arthroscopic fixation of the detachment fragment to its bed after debridement with two metallic screws.

Figure 10: X-ray showing screws' position just below the open physis in a skeletally immature patient.

Image: Osteochondritis dissecans can be a devastating disease to young athletes. A picture from Aspire Academy where Aspetar Hospital is providing medical care for their young athletes (illustration).

translating the same principles to fast isolation protocols from local cartilage donating areas to allow chondrocyte implantation in a single-stage procedure, allowing comparable results to ACI at a lower cost[38,39].

Osteochondral Allograft

Allograft tissue is also an available option to be considered in larger defects and cartilage revision procedures, yet more as fresh allografts in which superior chondrocyte viability is expected[2,40,41]. It enables the replacement of a pathologic osteochondral unit by competent, viable, and congruent cartilage regardless of its size[3].

Long-term follow-up clinical studies have demonstrated satisfactory outcomes using osteochondral allograft in treating OCD. Sadr et al[42] and Murphy et al[43] case series reported graft survivorship in more than 90% of patients at ten years, with high satisfaction and only 8% of graft failure.

Limitations to this procedure lie in the availability of tissue and government regulations on human tissues. Also, size matching, congruence, viability, and host-donor compatibility are to be considered. Thus, the successful implementation of this technique is limited to a few countries[3].

TAKE HOME MESSAGGE

OCD is a disease of the young population that restricts their activity and leads to undesirable outcomes if not treated or diagnosed early[10-12]. It should be suspected whenever the patient presents to the clinic with knee swelling or mechanical symptoms and not be overlooked[8].

Conservative treatment is the first-line treatment, especially in skeletally immature patients, and surgeons should be vigilant in their follow-up. Also, restricting activities in young patients is difficult, but the patient's family should be involved while this discussion happens in the clinic. Size, location, and bone edema are to be considered when managing activity restriction. Sports activity cessation and a quadriceps-strengthening program is the recommended conservative approach based on the available evidence and should be maintained for six months or upon resolution of primary radiological findings[16].

The final goal of treating this disease is maintaining hyaline cartilage to prevent osteoarthritis in the future[10]. History taking, physical examination, and Imaging modalities can help differentiate between different grades of the disease. The ultimate goal is to give the fragment the chance to heal by drilling or fixing it back to its anatomic position[24,44-47]. If the previous plans failed, surgeons should be familiarized with other restorative procedures. Then, the decision should be based on the size, depth, and location of the diseased fragment.

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MENISCUS ALLOGRAFT

HOW GOOD IS THIS OPTION?

– Written by Peter Verdonk, Belgium, Francesca De Caro, Italy, Jonas Grammens, Belgium, and Rene Verdonk, Belgium

OVERVIEW

The importance of the menisci in distributing load forces between the femoral and tibial bone, supporting the joint biomechanics as knee joint stabilizers while promoting synovial fluid distribution and cartilage nutrition, is well known to most orthopedic surgeons.

But still, in the USA alone, meniscectomy is estimated to be practiced on 850'000 patients yearly.

Meniscal tears are one of the most common injuries of the knee joint and result in significant loss of function. When they become symptomatic and irreparable, a partial meniscectomy is required.

Unfortunately, the functional loss of meniscus tissue as a result of tear, damage or surgery is proportional with the elevation of contact stresses on the cartilage surface, hereby risking early onset of cartilage damage. Hence, surgical removal of functional meniscus tissue should be limited.

The loss of functional joint tissue has irreversible consequences on knee homeostasis, especially in patients with already some degree of pre-existing osteoarthritis. The increased intra-articular contact stresses within the knee after meniscectomy resulting in 'overload' of the articular cartilage, ending with early articular cartilage degeneration, pain and functional limitations, that define the post-meniscectomy syndrome [1].

As a solution, surgical replacement techniques such as meniscal allograft transplantations (MAT) or the use of biodegradable scaffolds were introduced[2-3].

Meniscal allograft transplantation has evolved since the 1980s aiming to limit or even prevent the negative effects of meniscus loss. It is a possible treatment option for the patients with pain after meniscectomy, that have failed non-operative management. It has been shown to provide predictable symptomatic relief and a return to sporting activity with good long-term survival, and long term results continue to improve as surgical indications and techniques are evolving.

INDICATIONS

Correct patient selection is fundamental for successful meniscal transplantation surgery.

Appropriate candidates are young (typically less than 50-55 years old), healthy and active patients that are symptomatic after undergoing a prior meniscectomy and have failed further non operative management. A second indication is the patient with ACL instability in combination with a large meniscectomy, as the additional stabilizing role of the meniscus to the ACL has been well recognized.

The knee joint should be stable and limbs normal aligned. Grade I or II cartilage lesions are well tolerated, but any grade III or IV focal lesions might require concomitant treatment, whilst diffuse osteoarthritis (OA), squaring or flattening of the femoral condile, and significant osteophytes formation are clear contraindications.

Other contraindications include inflammatory diseases, previous infections, skeletally immature patients and marked obesity.

Varus/valgus malalignment or knee joint instability are relative contraindications and a two staged or concurrent surgery can be considered to ensure that all joint pathology is addressed.

Each patient should undertake radiographs of the knee including: antero-posterior and lateral weight bearing views, Rosenberg views and merchant (axial view of the patello-femoral joint) to exclude OA, and full length weight bearing x-rays to assess mechanical axis and a potential need for realignment. An MRI should also be obtained to evaluate the remaining meniscus, and most importantly to assess the cartilage and ligamentous status[4] (Table 1).

GRAFT SELECTION AND SIZING

A number of measurements techniques for the meniscus have been described

TABLE 1

Indications	*Contraindications*
Age < 50-55 y	*Age > 55 y*
Persistent unicompartmental pain, failure of non-operative treatments	*Knee instability*
Previous total or subtotal meniscectomy	*Generalized/grade-IV degenerative compartmental cartilage changes*
Outerbridge grade < 3 articular changes	*Marked radiographic changes such as femoral condyle flattening and osteophyte formation*
Correct alignment	*Varus/valgus malalignment*
No ligament laxity	*Synovial disease* *Inflammatory arthritis* *Obesity*

Table 1: Indications and contraindications to MAT.

based on plain radiographs, 3D computed tomography, magnetic resonance imaging and anthropometric data.

To date, the most used technique is the meniscal measurement obtained on a plain antero-posterior and lateral radiograph, as proposed by Pollard et al. On anteroposterior films two vertical lines are drawn perpendicular to the joint line and are used to measure meniscal width. In a medial meniscus, the first line is tangential to the medial tibial metaphyseal margin and the second is through the peak of the medial tibial eminence. For a lateral meniscus, the first line is tangential to the lateral tibial margin and the second is through the peak of lateral tibial eminence. The distance between these two lines is said to be meniscal width. Meniscal lenght is then measured in a similar manner on lateral radiographs. The first line is drawn at the anterior tibial surface above the tuberosity and the second is a parallel line tangent to the posterior margin of the tibial plateau[5].

For what concerns graft preservation, non-irradiated deep-frozen or fresh frozen, is one of the most common conservation methods used in orthopaedics. It can be stored at -80°C for up to 5 years. This method is technically simple and minimally immunogenic. The menisci, harvested under sterile conditions, are put into physiological solution with an antibiotic agent, followed by rapid freezing. Although donor fibrochondrocytes may be destroyed by the freezing process, it is hypothesized that the same process results in denaturation of the histocompatibility antigens and thus decreases immunogenicity within fresh frozen menisci. A further advantage is the maintenance of the mechanical properties of the meniscal allograft.

SURGICAL TECHNIQUE

Meniscal allograft transplantation (MAT) may be performed using either open or arthroscopically assisted techniques, or a combination of these, with a mini-arthrotomy to insert the graft and arthroscopic preparation and fixation.

Arthroscopically assisted techniques are obviously much more technically demanding, requiring a considerable learning curve[5-6].

The three main fixation methods that can be used to fix a MAT are: suture-only transosseus fixation, bone plugs fixation and the bone bridge technique. The first one consists of fixing soft tissue graft only using sutures through the body and meniscal horns, while the meniscal roots are fixed using a transtibial suture technique, similar to root lesion repairs. The bone plugs and keyhole techniques are different types of bone fixation. The double plug technique consists in bony fixation to the tibia of the meniscal horns, which are left attached to the allograft bone, and capsular fixation of the peripheral margin of the allograft. In the bone bridge technique, the grafts contain a common bone bridge attached to both anterior and posterior horns. This bone bridge is then inserted into a similarly shaped slot in the recipient tibia. It has been recommended that this technique should be used with implantation of a lateral meniscus because the distance between the horns is only 1 cm or less. Both osseous techniques require the preparation of osseous beds in the receptor knee, so the plugs or bridge can fit in it.

CONCOMITANT PROCEDURES

Meniscus allograft transplantation (MAT) has a significant role in the treatment of the symptomatic post-meniscectomized patient. However, the overall rules of surgical engagement include that in the presence of malalignment or ACL instability, a corrective osteotomy or an ACL reconstruction should be the first procedure, respectively, followed by MAT and ultimately cartilage repair. MAT or cartilage repair have little sense in the malaligned or unstable lower limb.

These concomitant procedures include a high tibial or distal femoral osteotomies when a malalignment is present, ligamentous reconstructions for unstable knees, and any cartilage procedure, such as microfractures, osteochondral allograft or scaffold implantation for focal cartilage defects. They should be performed at the time of the transplant, or via staged procedure, before the meniscal surgery[7].

Many studies evaluate the outcomes of meniscal allograft in conjunction with concomitant procedures, reporting no significant influence of these procedures on postoperative patient reported outcomes, failure rates and graft survivorship.

MAT AND SPORTS

The treatment of young, active patients with chronic pain after total meniscectomy remains clinically challenging.

Meniscus allograft transplantation results in athletes are good, with some authors reporting up to 70% of patients returning to the same level of sporting

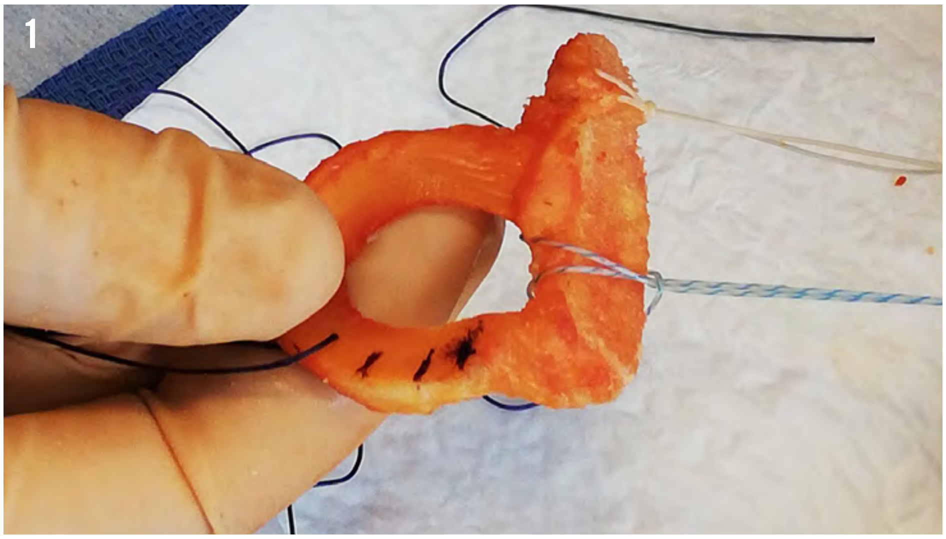

Figure 1: Lateral meniscus allograft with bone bridge connecting the anterior and posterior horn.

Figure 2: Medial meniscus allograft prepared for all soft tissue transosseus fixationusing bony tunnels and a posteromedial traction suture.

Figure 3: A typical lateral meniscus allograft patient presenting late. The lateral femoral and tibial articular cartilage already shows grade 4 cartilage defects. These cartilagenous defect are secondary to the loss of functional meniscus tissue. Earlier intervention with a lateral MAT could have avoided the advanced cartilage wear.

activities. But the most important aspect is the management of patients' expectations. The athletes undergoing this kind of surgery need to be informed that they will return to play in about 1.5 years. Moreover, they have to be aware that there is a possibility of progression of articular cartilage degeneration or of traumatic disruption of the meniscus implant. Despite these risks, MAT remains a moderately successful surgery in young sportive patients.

Higher-volume surgeons have significant lower rates of failure, so this athletic population should always be addressed to specialized surgeons[8-9].

A frequent observation in athletes confronted by meniscus damage and progressive cartilage degeneration is that most of these athletes are only referred for MAT in the later stages of the osteoarthritic disease when the damage in the affected knee compartment becomes very challenging (Figure 3). The ideal timing for MAT however remains an individual decision based on numerous parameters.

REHABILITATION

Refer to the 'Rehabilitation' Table.

RECENT INSIGHTS AND UNDERSTANDING OF MENISCUS DAMAGE PATHOGENESIS

The understanding of the pathogenesis of meniscus damage and tears, and the occurrence of early symptoms after meniscectomy is evolving. Meniscus disease is often the first symptoms of the onset of knee osteoarthritis. This disease is not only driven by a genetic predisposition but also by the mechanical load in the affected compartment. Hence factors such as activity level, body weight and alignment are essential parameters and can be addressed when dealing with the post-menisectomized patient.

Also a smaller size of the medial femoral condyle, and hence a smaller contact area and subsequently higher load, has been linked with early onset of meniscus tears and subsequent early onset of OA. Indeed, a recent study (submitted for publication) has observed that medial MAT patients have significantly smaller medial femoral condyles.

In addition, tabacco, smoking and shisha should be scrutenized as more studies have identified them as having a significant negative effect on healing of soft tissues.

REHABILITATION

Unloader brace	*Used for the first 3 to 6 months during walking and standing activities*
Weight bearing	*Weight bearing is limited to touch weight bearing for 3 weeks.* *Weight bearing is then gradually increased until full weight-bearing is commenced at 6 weeks*
Squatting and loading in deep flexion	*To be avoided for 6 months*
Isometric excercise	*Isometric quads and straight leg raise exercises can commence immediately post operatively, with closed chain exercises introduced at 6 weeks*
Cycling	*By 3 months exercising on a bicycle can be introduced*
Running	*To be avoided up to 9-12 months*

CONCLUSIONS

Meniscus transplantation is a reliable technique for younger patients exhibiting symptoms in their daily activities.

Long term results show improved knee function and pain relief in the majority of the patients up to ten years follow-up.

The results are believed to be more favourable when the operation is done before the onset of tibio-femoral arthritis. Again, well recognized indications and contraindications for meniscus transplantation have been previously described.

A correct surgical and fixation technique is crucial in order for the graft to provide load bearing function and possible chondroprotective effects. Minimizing extrusion of the graft, which supposedly puts it in a nonanatomic position leading to biomechanical disadvantages is important, even if studies have found no correlation between clinical scores and meniscal extrusion. A combined approach for lower limb malalignment and knee joint instability must be always taken into account.

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OSTEOTOMY, WHAT'S NEW?

– Written by Romain Seil, Dietrich Pape, Caroline Mouton, Luxembourg, Matthieu Ollivier, France, and Christophe Jacquet, Luxembourg & France

INTRODUCTION

For many athletes, high and repetitive joint loading may lead to knee joint degeneration either by acute trauma or repetitive overload. Traumatic knee injury causing ligamentous, meniscal, or cartilage damage can lead to focal degeneration. Excessive, repetitive joint loading may lead to osteoarthritis in the long term. A combination of both, as well as congenital or acquired limb malalignment may even exacerbate the problem of knee joint degeneration. If athletes become symptomatic and develop knee pain or posttraumatic instability or both, many non-surgical treatment options are available[1–3]. However, these options often fail to provide a sustainable solution, in which case surgical options should be considered. For recreational athletes, joint replacement surgery may be an option, mostly in non-pivoting sports. However, high- and elite-level competition in impact sports is not compatible with good long-term outcomes following joint replacement surgery. The use of joint-preserving surgical treatments like proximal tibial osteotomy (PTO) can be a suitable option for active patients and even allow for a high level sports practice in some selected cases. PTO is most frequently used to correct lower limb malalignment in the frontal plane in order to treat overload in either the medial or the lateral tibiofemoral compartment[4,5]. In more rare cases of specific knee instability, sagittal-plane PTO may be considered to compensate either for anterior (ACL) or posterior cruciate ligament (PCL) insufficiency.

Many athletes present with a varus morphotype, leading to an excessive loading of the medial part of the joint. In case of non-treated ACL or PCL injuries and associated intraarticular damage, biomechanical changes do often even increase varus loading, thereby exacerbating the degenerative process of the medial tibiofemoral compartment. In patients with symptomatic medial compartment overload or osteoarthritis, a bony realignment procedure in the frontal plane may therefore be indicated to decrease varus loading. In most cases, the varus deformity is located at the proximal tibia, which is the reason why PTO is a good surgical option for these patients. The rare cases of varus knees in which the deformity is located at the distal femur should be ruled out. If a PTO is performed in these patients, a lateral inclination of the joint line may occur, thus increasing the risk of an unsuccessful outcome. In these patients, as well as in most patients presenting with the much rarer lateral tibiofemoral overload or osteoarthritis, deformity correction may require a distal femoral osteotomy (DFO).

The aim of sagittal plane corrections is to modify the tibial slope, either by increasing or decreasing the inclination of the tibial plateau. Slope-changing PTO is a powerful tool to balance the knee in the sagittal plane by altering the position of the tibia underneath the femur. In ACL deficient knees, a decrease of the tibial slope can decrease anterior tibial translation (ATT)[6,7], because an excessive tibial slope is an established risk factor for ACL injuries and recurrences[8,9]. This procedure may be required in some cases of repeat ACL revision surgeries. Likewise, an increase of the slope increases Anterior Tibial Translation and is therefore a valid alternative for chronic PCL-deficient knees[10]. In exceptionally rare and very challenging cases, corrections in both the frontal and sagittal plane can be combined.

In the past, the most preferred PTO was a lateral closing wedge osteotomy (LCWO), but over the last 2 decades,

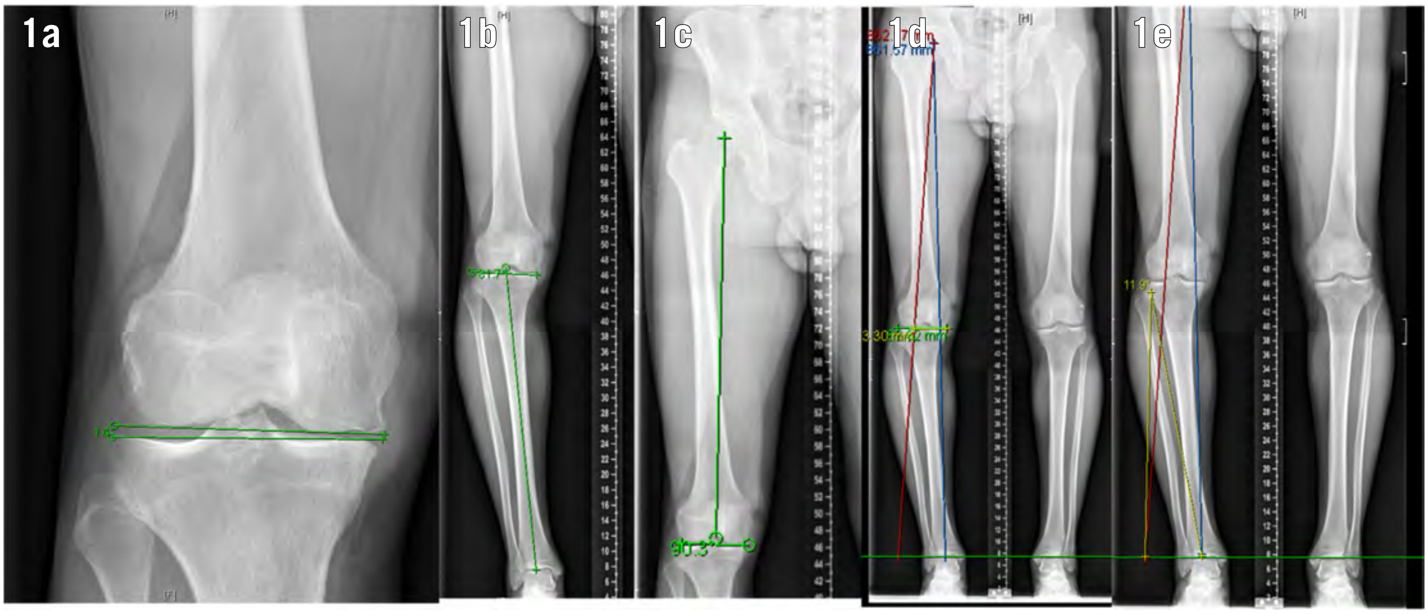


Figure 1: Measurement of angles. (a and b) Medial Proximal Tibia Angle (MPTA) and Joint Line Congruency Angle (JLCA). (c) Lateral Distal Femoral Angle (LDFA). (d and e) Calculation of the needed correction using the Miniaci Method: we first draw the lower limb weight bearing line (blue): line passing from the center of the hip to the center of the ankle. A second line (red) connecting the hip center, passing through the selected "Fujisawa" point and crossing a line parallel to the ground and passing through the center of the ankle is drawn as well. A line (yellow) connecting the future tibial hinge point and the center of the ankle joint is given is drawn. Similarly, another line (yellow), connecting the future tibial hinge point and the intersection of the red line with a line parallel to the ground passing through the center of the ankle joint is drawn. The angle formed those lines going from the native ankle position and the future (after correction) ankle position, crossing at the hinge level represents the predicted correction angle (angle α).

medial opening-wedge PTO (MOWO) has undergone a rapid evolution[11] and gained in worldwide popularity. The reasons for this are a decreased intra- and perioperative morbidity, which is mainly due to the development of powerful internal fixator plates displaying a high primary stability. In comparison to LCWO, MOWO techniques do also induce lesser anatomical changes of the proximal tibia and avoid the need of an associated fibular osteotomy, a frequent cause of intraoperative morbidity and persisting postoperative pain. A growing number of studies have reported good post-operative outcomes of MOWO with very low (< 5%) complication rates[5]. The aim of this publication is to summarize the indications and principles of multiplanar PTO, including the 3D pre-operative planning for MOWO and to present the post-operative outcome of active patients.

SURGICAL PLANNING

a) MOW-PTO

Thorough and precise surgical planning is required in order to achieve best possible surgical accuracy. This is especially mandatory in complex cases with combined problems associating OA and pathologic ligament laxities. It has been shown that an accurate correction in all three spatial planes is a pivotal factor to obtain good clinical outcomes[12]. To achieve ideal correction, various planning methods and surgical techniques have been developed. Conventional radiographic measurement methods, various intraoperative techniques to assess lower-limb alignment, computer-assisted surgery (CAS)[13,14] and recently the use of patient-specific cutting guides (PSCG)[15–17] are all useful to help the surgeon achieve the best possible accuracy.

In the vast majority of cases frontal plane PTO aims to correct an extra-articular deformity by shifting the mechanical axis from the affected tibiofemoral compartment to the other in order to unload cartilage and subchondral bone[18]. In those cases, natural evolution of knee arthritis might be slowed down by correcting a pre-existing tibial or femoral metaphyseal abnormality.

Planning should be performed on bilateral long-leg weight bearing X-rays, ideally with the patella centered in the middle of the knee and a forward orientation of the feet[19]. On these radiographs, the Hip-Knee-Ankle (HKA) angle is used to estimate the overall alignment of the lower limb. This angle is the result of three components, which are the bony alignment of the femur, the bony alignment of the tibia and the intra-articular deformity resulting of articular surface wear and soft-tissue laxity. Two additional angles are mandatory to establish the bony alignment of the distal femur and the proximal tibia: (a) The lateral distal femoral angle (LDFA), which is defined by the angle between the femoral mechanical axis and the articular surface of the distal femur and (b) The medial proximal tibial angle (MPTA), which is defined as the angle between the mechanical axis of the tibia and the articular surface of the proximal tibia. Finally, it is also recommended to measure the Joint Line Congruency Angle (JLCA) which best reflects cartilage wear, meniscus loss and soft-tissue laxity. (Figure 1 a,b, and c).

When dealing with a malaligned lower limb, the next step is to establish the desired postoperative alignment and therefore to plan the desired correction. Early studies of valgus PTO's led to the concept that the postoperative, ideal weight-bearing line should be within 62% and 65% of the lateral tibial plateau (with the medial side set at 0% and the outermost lateral aspect at 100%)[20] However, this did often result in severe overcorrections in the frontal plane as well as negative, laterally inclined joint line angles. Therefore, more recent studies[21] recommended to adapt the degree of correction to the degree of OA, thereby resulting in a lesser degree of frontal overcorrection. (Figures 1 d and e). Once the desired correction point has been determined, the amount of needed correction can be calculated according to well-established planning methods. The most popular one has been described by Miniaci and Jakob[22] (Figures 1 d and e).

b) Slope-changing PTO

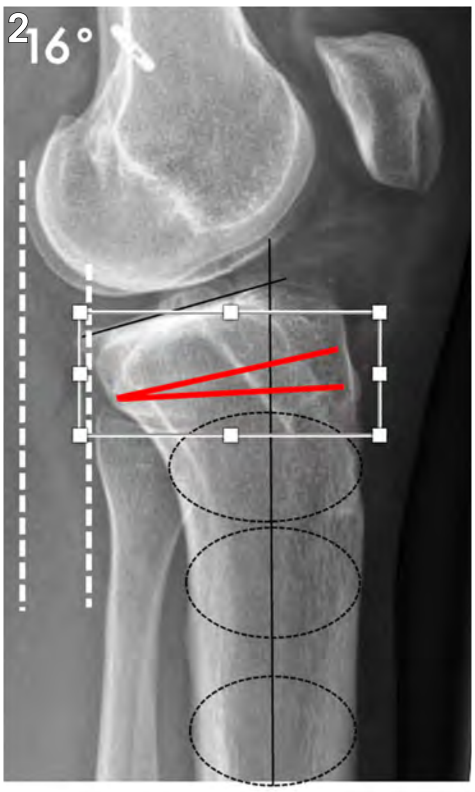
In patients where slope corrections need to be performed, a different planning strategy is needed (Figure 2). In the routine clinical setting, the measurement method popularized by Dejour on short lateral views is recommended to evaluate the slope of the concave, medial tibial plateau. In a Caucasian population, a value of 12° is the threshold above which the tibial slope is considered being a risk factor for primary and recurrent ACL injuries[23]. If a slope-correcting PTO is required, lateral long leg standing views are recommended in order to visualize the entire bone. Surgical planning is performed according to the principles of deformity correction popularized by D. Paley[24]. In ACL deficient knees with excessive tibial slope, the aim of the surgical procedure is to correct the tibial slope to a normal value close to 7°[25]. However, it must be emphasized that knee recurvatum is increased by a slope-decreasing extension PTO. In these cases the amount of recurvatum increase will correspond to the degree of correction, in other words the height of the anterior wedge (Figure 2). A recurvatum deformity of > 10° is therefore considered being a contraindication for this type of procedure. In patients with a PCL deficiency, the tibial slope needs to be increased to allow to reduce posterior sagging of the tibia. This treatment is usually reserved for patients in whom PCL reconstruction cannot be considered which is the case for irreducible and fixed grade 3 PCL insufficiencies (Figure 3). A 5° slope increase is generally enough to neutralize posterior tibial translation after chronic PCL insufficiency[10], without increasing strain on the ACL.

In patients with previous surgeries and planned associated procedures, additional diagnostic methods like CT scans may be required to identify adequate hardware placement and to define the bone quality and the position of bone tunnels created by previous surgeries.

SURGICAL TECHNIQUES

a) MOWO[26]

For MOW-PTO, the procedure starts with adequate soft tissue management. A skin incision of approximately 7 cm starts 1 cm distal to the medial tibiofemoral joint line and extends towards the distal tibia. Identification of the anterior tibial tuberosity and the attachment of the patellar tendon as well as the pes anserinus with the underlying medial collateral ligament (MCL) are the first steps of the procedure. The pes anserinus is dissected and retracted posteriorly. The MCL is released subperiostally and a Homann retractor is placed around the posteromedial tibia (Figure 4). This elevator is left in place to guide the posterior-tissue retractor (PTR) between the posterior cortex and the popliteus muscle (Figure 5). At this step of the procedure, 2 Kirschner wires are introduced under fluoroscopy, running from the proximal border of the pes anserinus and the concavity of the proximal tibia metaphysis towards the superolateral tibia plateau and the proximal end of the fibular head. The wires should run parallel to the concavity of the medial tibial plateau. An oscillating saw is used to perform the



3a

3b

Figure 2: Example of a planning of an extension osteotomy for chronic ACL insufficiency.

Figure 3: (a and b) Example of a flexion osteotomy for chronic PCL insufficiency.

biplanar osteotomy. During the horizontal cut care must be taken not to violate the popliteal vessels. During the vertical cut, the patellar tendon should not be injured. Various techniques such as PSCG, CAS, fluoroscopy can be used to guide the saw and to improve the accuracy of the correction. The saw cut is then completed by specific osteotomes taking care to preserve an intact lateral bone bridge of approximately 1 cm (lateral hinge). The opening of the osteotomy is performed by placing a laminar spreader at the posteromedial border of the tibia. Before this step, it is mandatory to control the tibial slope. In order to avoid slope change, the geometry of the proximal tibia requires a trapezoidal opening with the large end being at the posteromedial corner of the osteotomy (Figure 6). The osteotomy gap can be filled with allograft bone or left in situ. When the desired opening has been achieved, the osteotomy is secured with a locking plate.

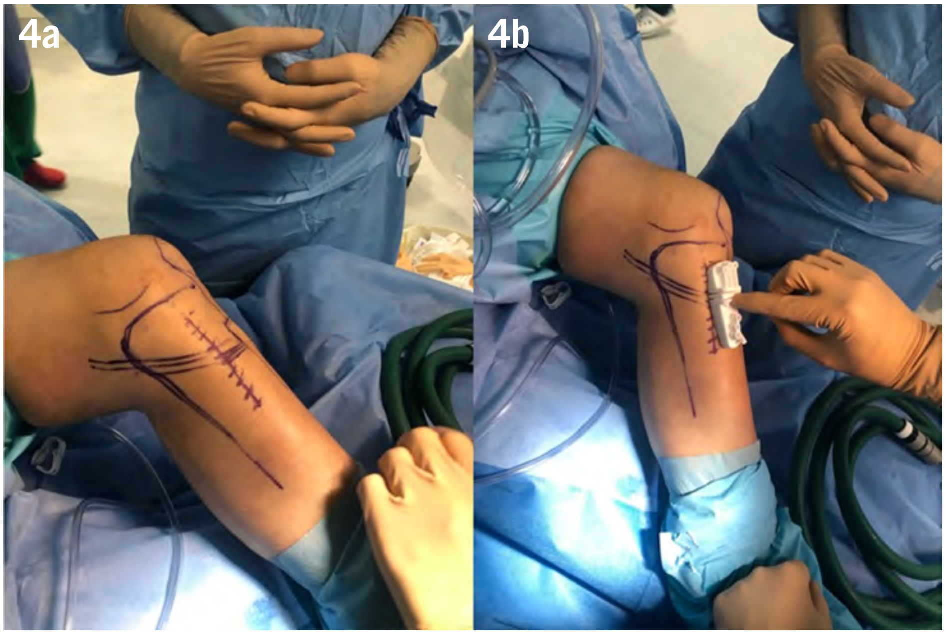


Figure 4: (a and b)Medial approach for the osteotomy: starting 1cm below the femoro-tibial joint line and extending 8-10 cm toward the distal tibia.

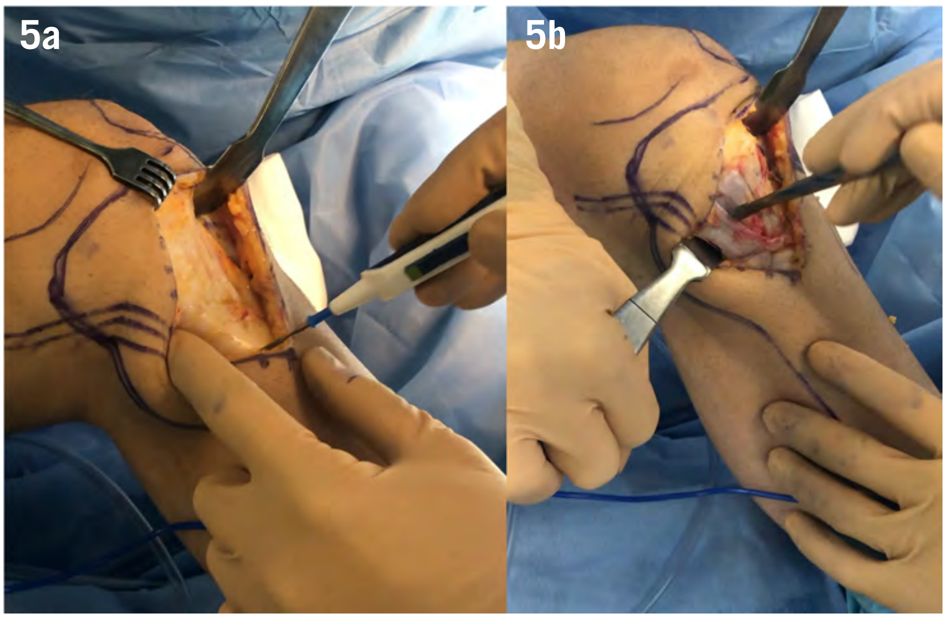


Figure 5: (a and b) Medial approach for the osteotomy: : the pes anserinus is dissected and retracted posteriorly. Starting at the posterior aspect of the MCL a periosteal elevator is used to dissect the soft tissue until the posterior cortex of the tibia is reached and the popliteus muscle carefully released. This elevator is left in place to guide the posterior-tissue retractor (PTR) between the posterior cortex and the popliteus muscle (this step can be done in flexion to facilitate insertion).

b) Slope-increasing OW-PTO

Most of the surgical procedure is the same if an increase of the tibial slope is to be achieved. However, in order to be able to induce a sagittal plane correction, a controlled section of the lateral hinge is recommended. This should be done under fluoroscopic control. For osteotomy opening, the laminar spreader needs to be placed anteriorly, thus inducing a triangular osteotomy shape at the medial tibia, with posterior compression and anterior opening.

c) Slope-decreasing PTO

The rare slope-decreasing, anterior closing wedge osteotomies are usually performed in conjunction with a second or third ACL revision reconstruction, hence combining the complexity of 2 challenging procedures. We perform these procedures on a hanging knee in a supine position and a mobile leg holder. Arthroscopic intraarticular steps are conducted first to address potential meniscus or cartilage problems, to eventually remove hardware and perform femoral ACL tunnel management. The supratuberosity PTO is performed through an 8-10 cm midline incision. Soft tissue identification includes the patellar tendon and medial as well as lateral soft tissues of the proximal anterior tibia. K-wires are inserted in an anteroposterior direction under fluoroscopy and serve for wedge height determination as well as estimation of the depth of the saw blade. Bone resection is done under fluoroscopy, taking care to leave the posterior cortex intact. After wedge resection, the osteotomy is closed anteriorly through gentle manual compression and fixed with either screws or staples. Finally, ACL revision reconstruction is finalized through tibial tunnel management, graft passage and fixation.

REHABILITATION

Postoperative management includes toe touch weight bearing for 6 weeks aided with the use of crutches (50 % body weight). Full weight-bearing is allowed at 6 weeks. Usually there is no restriction on the range of motion and no brace is used. A drain without suction is left in place for 24 hours. Patients receive thromboprophylaxis with low molecular-weight heparin for 45 days.

Dynamic evaluation using a dedicated motion capture engine is performed at 6 months post-surgery to analyze the biomechanical modifications during walking and running (Figure 7).

DISCUSSION

PTO is an effective procedure for the surgical management of several degenerative knee conditions like medial compartment overload or OA in varus malalignment[27–29]. In many patients it allows to preserve the joint, provides patients with good functional conditions and buys time before considering knee arthroplasty. In some more rare cases in patients with cruciate ligament deficiencies, it is a powerful tool to balance the knee in the sagittal plane[30–33].

Patients can reasonably expect to perform activities of daily living and recreational sports without debilitating pain or instability. We analyzed the ability of active patients to return to impact sports after PTO and unicompartmental knee

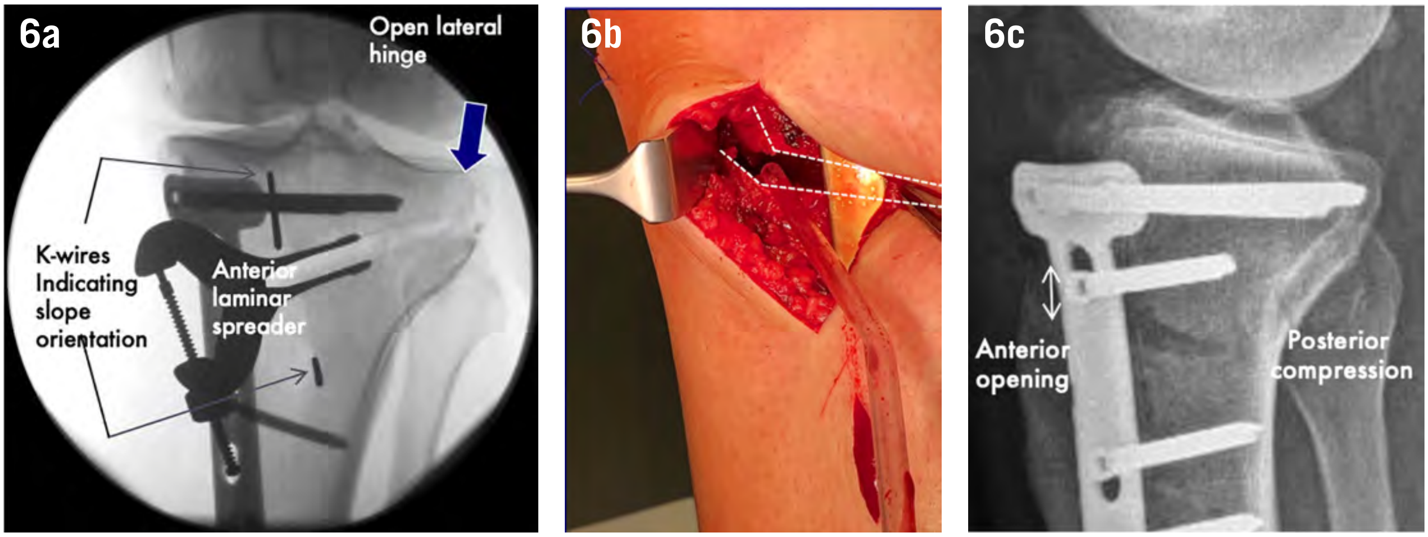


Figure 6: (a-c) Example of an extension osteotomy for chronic ACL insufficiency.

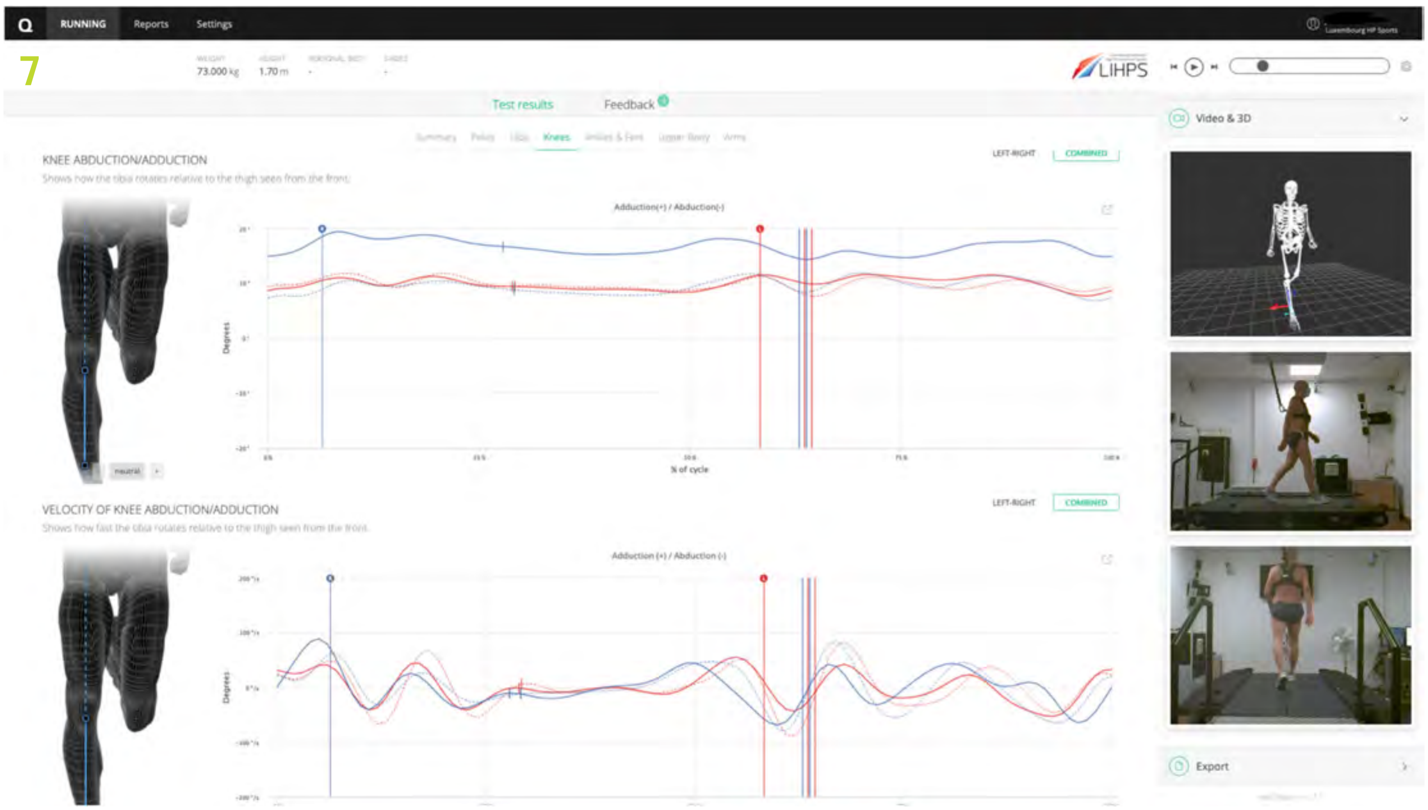


Figure 7: Dynamic evaluation using a motion capture engine at 6 months post-surgery after a double level osteotomy (PTO + DFO) for grade III medial OA and varus deformity.

arthroplasty (UKA) procedures[17]. Irrespective of their sporting level, the mean time to return to sports and previous professional activities was significantly lower in the PTO group (4.9 months for PTO group vs 5.8 months for UKA group and 3.0 months for PTO group vs 4.0 months for patients with a UKA). Twenty-four months after surgery, a significantly higher amount of patients who underwent a PTO were practicing impact sports (62 vs. 28%) and PTO patients had significantly better sports-related functional scores. These findings were in accordance with Bastard et al[34] who observed that all of their 30 patients treated with PTO returned to sports at 1 year; with 7 (23.3%) of them returning at a higher level than before the procedure. A systematic review by Ekhtiari et al[35] reported similar findings, with 85% of the 216 patients returning to a level of sports practice which was similar or better than before surgery. Salzmann et al[36] identified that the 3 preferred sports types after a PTO procedure were cycling (71%), swimming (45%) and hiking (30%). Another recent study[37] indicated that active sports participation in the year before surgery is one of the most important prognostic factors for returning to sports after HTO. These results do also suggest that operating high impact sport patients at an earlier stage of osteoarthritis with PTO may provide them with a higher probability to recover an activity level which can be expected to be similar or close to the one they had before the onset of osteoarthritis.

Does associating cartilage and meniscus repair surgeries improve the results of PTO ?

Focal articular cartilage defects and meniscal deficiency, either individual or in combination, are often associated with unicompartmental overload, especially if a frontal alignment deformity is associated. Performing an isolated cartilage or meniscal repair procedure in these patients may increase the risk of failure. For these reasons, adding a PTO to the intraarticular soft tissue procedure in case of focal cartilage defects or repairable meniscus tears with the ultimate goal of joint preservation seems mandatory from a biomechanical perspective. However, to date there is limited evidence that associated cartilage or meniscal repair procedures will add a significant benefit to the PTO. In a study comparing isolated Autologous chondrocyte implantation (ACI) with a combined ACI and PTO procedures in patients with varus deformity and local chondral defects, Bode et al[38] observed better outcomes in the combined ACI and PTO group compared to the isolated ACI group. However, one of the limitations of this study was the lack of a control group of patients with isolated PTO to ensure that this improvement was not exclusively due to the PTO procedure. In another study, Harris et al[39] tried to determine survival and clinical outcomes of PTO with or without articular cartilage surgery and/or meniscal allograft transplantation in patients with medial compartment chondral pathology, varus malalignment, and/or meniscal deficiency. They observed that survival and clinical outcomes of isolated PTO and PTO with associated intraarticular surgery were similar. In a meta-analysis published by Elattar et al[40], by analyzing 135 associated meniscus allograft transplantations with PTO procedures, the authors concluded that there was no clear scientific evidence of the synergetic protective relationship between meniscal allograft transplantation and unloading osteotomy in post-meniscectomy patients with malalignment. So there is no strong evidence to date that associated chondral reconstruction or meniscus repair procedures provide any benefit over isolated PTO, thus indicating that the biomechanical effect of PTO may be the major determinant for a successful outcome. Further studies are needed to standardize indications, select patients and analyze the short and long-term outcome for PTO in association with intraarticular soft tissue reconstruction procedures.

Is PTO a reasonable surgical option for high-level athletes?

PTO may provide a solution for athletes with underlying knee malalignment and symptomatic degenerative conditions in isolation or in association with ligamentous insufficiency who desire to continue competing at a high level. However, published evidence on the subject is sparse and none of the previously cited studies focused on elite athletes or addressed the athletes' ability to return to competitive

> ***Proximal tibial osteotomy is a powerful joint preservation surgery in physically active patients where cartilage or meniscus preservation procedures are insufficient or inappropriate. In some selected cases, it may allow for a return to high level sports practice.***

sports after surgery. At the end of an athletic career where athletes do often present with significant degenerative changes in their knee joints, PTO may help to prolong activity for a limited amount of seasons after a thorough postoperative return to play process. The cases of athletes achieving successful careers after PTO in the early stages of their career are anecdotal. Warme et al[41] described the case of a young collegiate American football player who returned to play and eventually entered an NFL team after a failed attempt of isolated fixation of an OCD lesion of the medial femoral condyle and later successful autologous chondrocyte implantation, combined with a PTO to off-load the medial compartment and better facilitate healing of the OCD lesion. In our own experience, the example of the female football player (case no. 4) illustrates the possibility to return to football after PTO in a neutrally aligned limb which was brought to slight valgus alignment. It is questionable if this experience would be similarly successful in a football player with varus alignment in whom a realignment procedure may negatively affect the individual playing technique. On the opposite, it might be successful in a type of sport that is less dependent on pivoting activities. These examples depending on gender-related alignment and type of sport illustrate the uncertainty of results in this specific subpopulation. Further studies are needed to standardize the indications and to better predict postoperative results in high level athletes.

CONCLUSION

PTO is a suitable surgical option for patients with early knee monocompartmental osteoarthritis and malalignment when nonsurgical management has failed. It can be performed in isolation or in association with ligament surgeries like ACL reconstruction. In comparison to joint replacement surgery, PTO allows for a higher return to impact activities (62% for PTO) and better sports related functional scores. In more rare cases, PTO can be used for tibial slope corrections in patients with chronic ligament insufficiencies. Evidence for PTO's in high level or professional athletes is sparse, but it may be an option for rare and selected cases. Further studies are needed to standardize indications and evaluate the outcome in these demanding patients.

CASE DISCUSSIONS

Case 1: PTO for varus malalignment and early medial tibio-femoral osteoarthritis (Figure 8)

The first case demonstrates the use of PTO in the treatment of early medial knee osteoarthritis and varus deformity in a 51 year old male patient. Seven years before he underwent a partial medial meniscectomy for a degenerative meniscus lesion. He developed medial knee osteoarthritis with significant pain during walking. Physical examination revealed varus alignment and medial joint line tenderness without sagittal or frontal laxity. Radiographic imaging at presentation showed degenerative changes of the medial compartment (Ahlback 2), and a varus deformity of 8 degrees located in the proximal tibia (MPTA: 80°/ LDFA :92°).

A MOWO was recommended in order to correct the frontal extra-articular deformity and overload of the medial compartment .

Case 2: PTO for post-traumatic chronic PCL deficiency (Figure 9)

The second case demonstrates the use of PTO in the treatment of chronic PCL deficiency and varus malalignment. The patient was a 33 years old recreational athlete. Six years before he sustained a football accident with a direct trauma due to a collision with another player. A grade 3 PCL injury was diagnosed and treated non-surgically. The patient stopped playing football developed a painful and fixed posterior subluxation. Radiographic imaging at presentation showed no major degenerative changes of the medial compartment, and a bilateral varus deformity of 2°. The sagittal X-ray demonstrated a grade 3 side to side posterior laxity with a 12 mm posterior tibial translation at stress x-rays in 90° of flexion and a tibial slope of 7°. The patient used crutches for daily walking because of

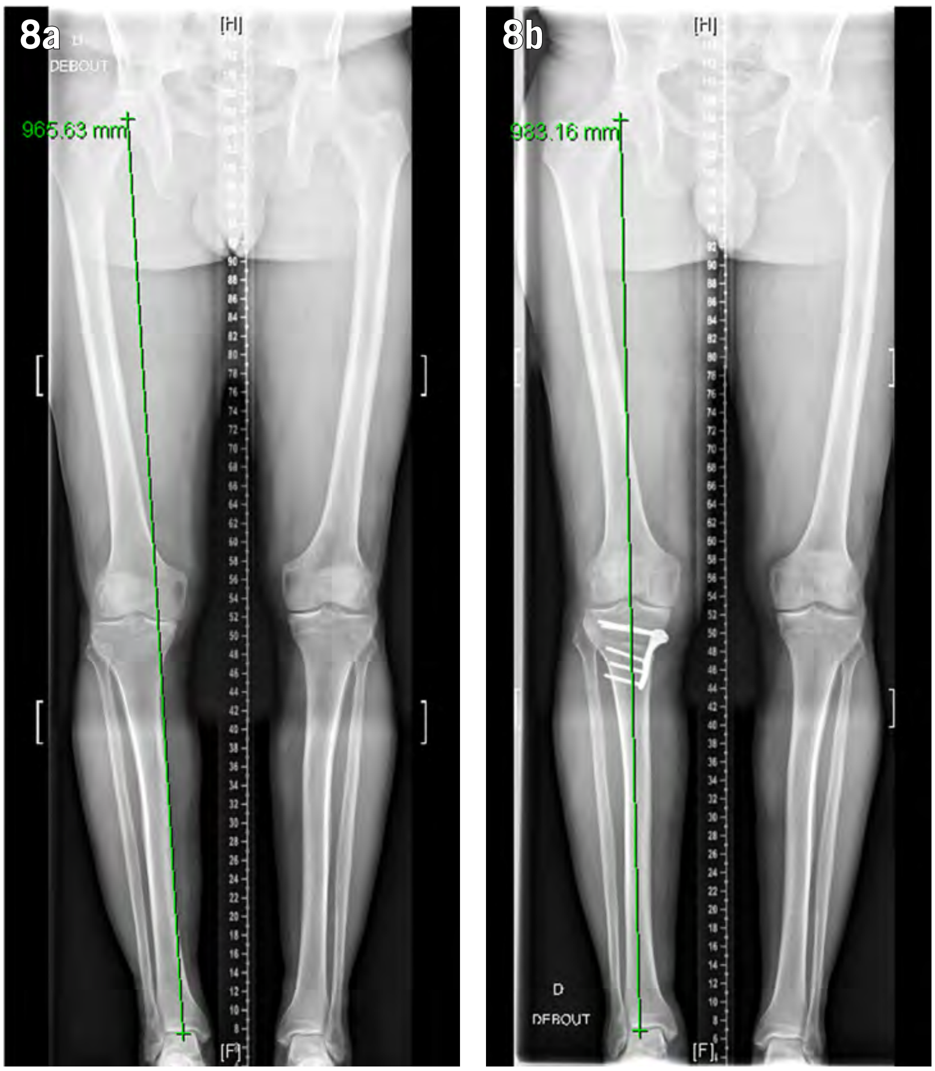


Figure 8: (a and b) Pre-operative and postoperative x-rays of the Case 1.

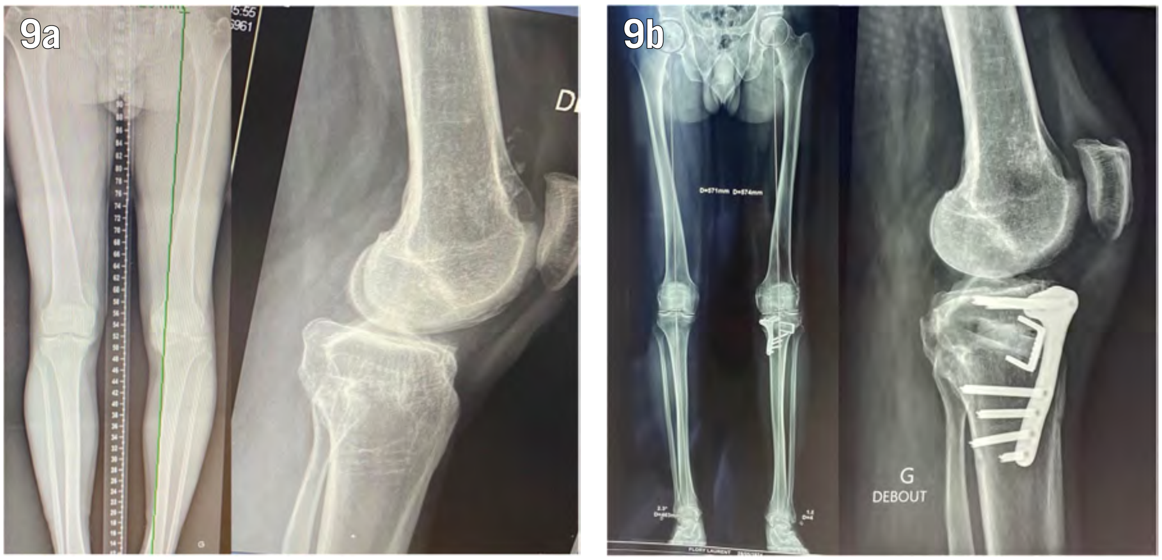


Figure 9: (a and b) Pre-operative and postoperative x-rays of the Case 2.

Figure 10: (a-c) Preoperative and postoperative X-rays of the case 3.

pain. Physical examination revealed slight varus alignment and posteromedial joint line tenderness. Range of motion was free. There was no pathologic posterolateral or posteromedial laxity. Because the posterior tibial translation was reducible during physical examination, a reduction test with a dynamic PCL brace was attempted for 3 months without success. Flexion osteotomy was therefore recommended to reduce the fixed posterior translation, thereby increasing the tibial slope to 15°, without changing the frontal alignment. At 3 years postoperatively the patient is pain free and resumed a normal life. He is able to perform manual work and participate in leisure sports activities. Spontaneous posterior tibial sagging has disappeared and monopodal stance radiographs show an improvement of posterior tibial translation of 12 mm.

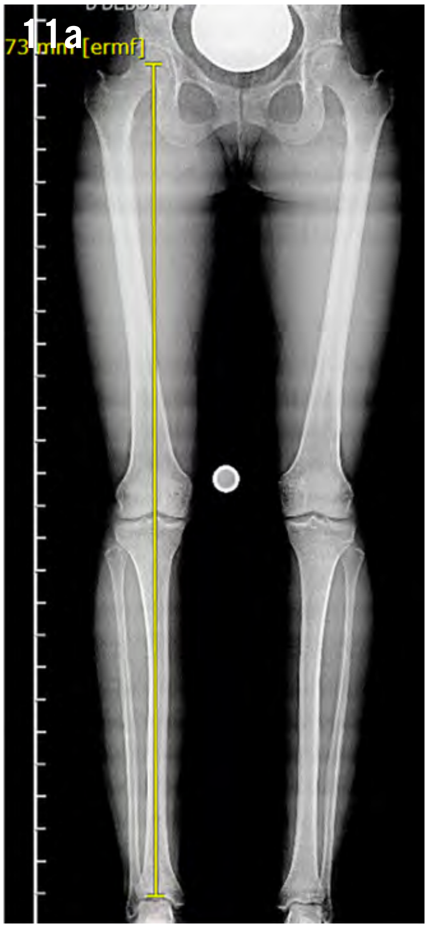
Case 3: PTO for ACL reconstruction failure without frontal-plane malalignment (Figure 10)

The third case demonstrates the use of PTO in the treatment of ACL graft failure with excessive tibial slope and with normal limb alignment in the frontal plane. The patient was 31 years old and had an ACL injury few years before. He was operated a first time with an isolated ACL reconstruction and a second time for an ACL graft rupture. A second rupture of the graft occurred during a minor trauma. Clinical exam revealed subjective symptoms of instability, a positive Lachman test (++) and a positive pivot shift test (++) without frontal deformity. MRI imaging confirmed the second rupture of the graft without associated meniscus injuries. Radiographic imaging showed an HKA angle of 181° and a tibial slope of 14°.

A concomitant slope decreasing osteotomy with an ACL reconstruction using allografts was performed to treat the sagittal instability and to reduce the risk of a third graft rerupture.

Case 4: PTO to treat a focal chondral defect (Figure 11)

The fourth case demonstrates the use of PTO



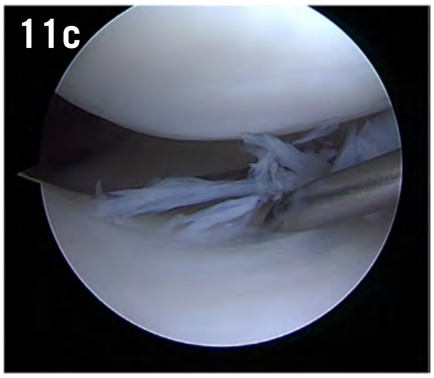


Figure 11: (a-d)Preoperative and postoperative images of the Case 4.

in the treatment of a focal chondral defect in a female professional football player. The patient was 27 years old and presented with a symptomatic isolated grade 4 focal chondral defect of the medial tibia plateau with pain during activities of daily living and inability to play football. The full leg x-ray shows a neutral limb alignment and the MRI confirms the medial tibial chondral defect. Non-surgical treatment failed to treat this lesion. A first arthroscopic evaluation with a debridement and microfracturing of the lesion did not improve symptoms. Therefore, a valgus MOWO was performed to unload the medial compartment. At 9 months after surgery, the pain disappeared and the player returned to football.

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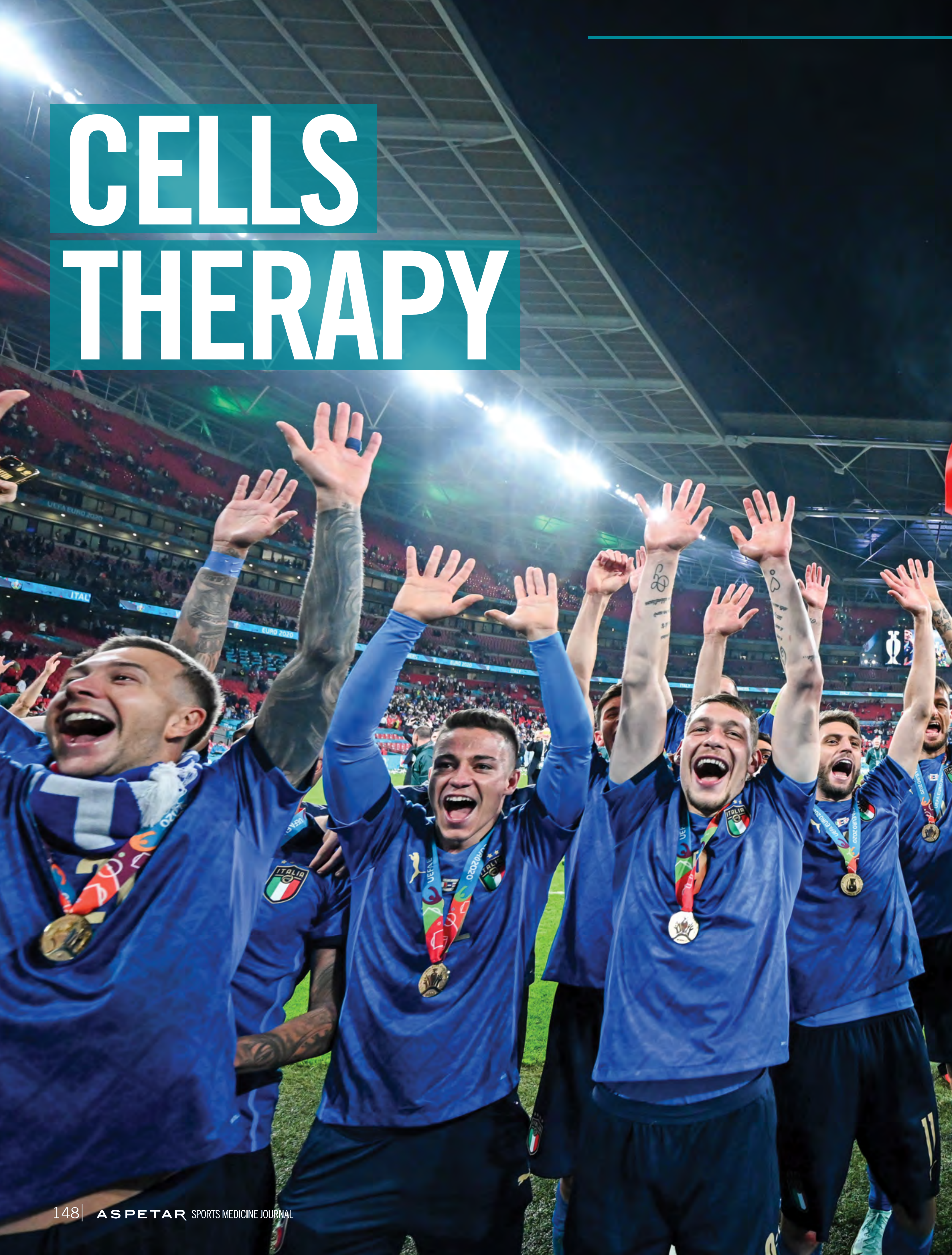
CELLS THERAPY



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THE CHONDROCYTE; STILL VALUABLE FOR CARTILAGE REPAIR

HISTORY AND NEW ACHIEVEMENTS

– Written by Mats Brittberg, Sweden

INTRODUCTION

Musculoskeletal injuries with traumatized tissues are resulting in a bleeding, blood clot formation and an ingrowth of repair cells into the blood clot scaffold[1]. Cartilage being devoid of blood vessels and nerves will not have a chance of such repair with just a few cells migrating into the defect and no messenger to instruct a start of a reparative process[1]. Numerous attempts have been performed to increase the reparative ability of cartilage with most of them involving bone marrow stimulation (BMS) and by that induction of a bleeding with subsequent blood clot scaffolding to attract cells from the bone marrow to repair the defects[2,3,4].

Small defects have been treated by BMS alone while larger defects have been augmented by artificial scaffolds to improve the filling[2,3,4,5,6]. For long, it has been thought that the bone marrow cells are repair cells while recent studies tell us that those cells are more of medicinal signaling cells stimulating the cartilaginous surrounding and synovia[7]. Recently, Arnold Caplan suggested a change of the name of MSCs from mesenchymal stem cells to Medicinal Signaling Cells to better reflect the fact that these cells home in on sites of injury or disease and secrete bioactive factors[7].

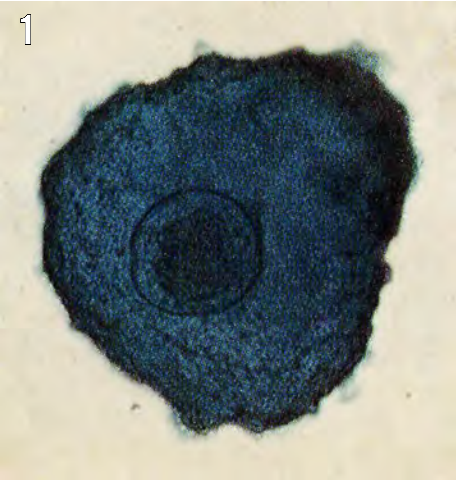
The chondrocyte (Figure 1), the one and only cell in cartilage is being responsible for all matrix production and would be the most natural cell to use when to repair cartilage defects[8,9]. When chondrocytes are separated from their matrix, the cells could divide, proliferate and become more in numbers[10]. Enzymatic digestions of cartilage and in vitro cell expansions are used when to culture chondrocytes to use them as cell source for cartilage repair[10,11].

The clinical use of chondrocytes

The first clinical use of chondrocytes for clinical cartilage repair was performed in Gothenburg, Sweden in 1987 (Brittberg et al 1994)[12].There exist today long-term results up to 20 years with good results based on the 1st generation ACI with chondrocytes in suspension implanted under a periosteal membrane[13-16].

Today in 2021 we have now 4 generations of ACI:

- 1st generation ACI: Chondrocytes in suspension injected under a living periosteal membrane[12] (Figure 2).
- 2nd generation ACI with cells in suspension injected under a collagen membrane[17].
- 3rd generation of ACI with cells either grown on a surface carrier[18] or cells grown in a porous matrix/scaffold[19]. To this generation also scaffold-free ACI is categorized[20].
- 4th generation ACI is when chondrocytes are in different ways implanted as one-stage procedures. Examples are when chondrocytes are directly isolated and mixed with directly isolated autologous MSCs[21] or allogeneic MSCS seeded in a matrix[22]. Fourth generation ACI are also variants of particulated or minced autologous or allogeneic cartilage on scaffolds



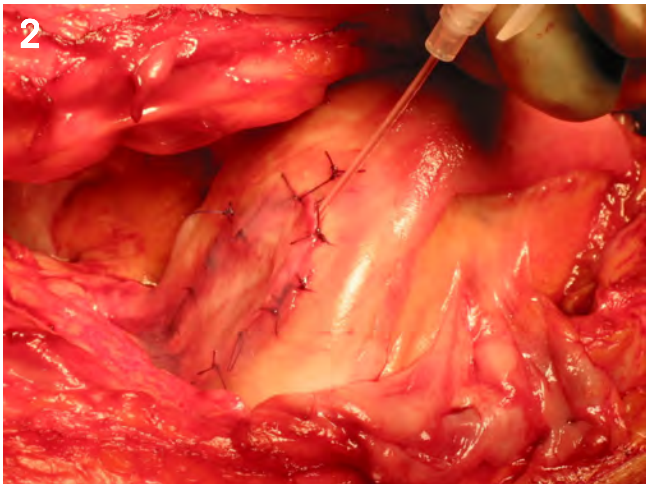


Figure 1: A chondrocyte in cell culture. Alcian-Blue.

Figure 2: Chondrocyte implantation under a periosteal flap-1st generation ACI.

(CAIS[23], CAFRIMA[24], AutoCart®[25], and DeNovo®[26]).(Figure 3 a and b).

Cell therapies including cultured chondrocytes are examples of cell manipulations and such modulations are requiring special regulatory frameworks developed by FDA[27] in USA and EMEA[28] in Europe. The way to be approved for cell therapies is long and very expensive and many companies involved in cartilage repair have tried to find cell therapies not involving cell manipulations and by that much easier to use for the surgeons with less costs. Subsequently, today very few in vitro expanded chondrocytes techniques are available for the patients. Commercially available ACI Gen III techniques today in 2021 are:

- MACI®[29]-Vericel USA.
- Bioseed-C®[30] – BioTissue Germany.
- CaRes- Arthro®[31] Kinetics Biotechnology GmbH (Austria).
- Chondrosphere®[32] (spherox)-CoDon Gemany.

In clinical trials:

- Hyalograft-C-HS[33].
- NeoCart®[34]-Histogenics (USA).
- NovoCart®[35]-Aesculap biologics.

Other chondrogeneic cells

Instead of using manipulated cells, the companies have focused on the use of different chondrogeneic cells for repair, cells that can be used as one-stage procedures. Both chondrocytes but also cells not being pure chondrocytes could be used for cartilage repair.

Non chondrocyte Chondrogeneic cells are:

- Bone Marrow-Derived Stem Cells[36,37].
- Adipose-Derived Stem Cells[38].
- Synovial Membrane-Derived Stem Cells[39].
- Muscle-Derived Stem Cells[40].
- Peripheral Blood Stem Cells[41].
- Menstrual blood progenitor cells[42].

Those adult stem cells have limited self-renewal capacities. Furthermore, as a person ages, these cells exhibit decreased proliferation rates and lessened chondrogeneic differentiation potential.

Figure 3: (a) Cartilage fragments have been harvested trans-arthroscopic with a shaver and a special cartilage fragment collector (Graftnet collector-Arthrex).The fragments are shown in the collector and will be implanted into the joint. (b) A cartilage defect, first as empty defect and then after filling with cartilage fragments in fibrin glue.

Furthermore, also extra embryonic sources of cells to be used exists such as[43]:

- Wharton's Jelly Stem Cells.
- Umbilical Cord Blood Stem Cells (BMP-2, BMP-6).
- Amniotic Fluid Stem Cells.
- Placenta-Derived Mesenchymal Stem Cells.

A study compared human MSCs derived from bone marrow, Periosteum, Synovium, skeletal muscle and adipose tissue[44]. The study revealed that synovium-derived MSCs exhibited the highest capacity for chondrogenesis, followed by bone marrow-derived and periosteum-derived MSCs.

Furthermore, it has been shown that culture-expanded chondrocytes have the potential[45] :

- to form cartilage in in vitro pellet mass cultures,
- to form adipose cells in dense monolayer culture,
- to form a calcium-rich matrix in an osteogenic assay.

Important finding was, however that in contrast with MSCs, chondrocytes formed cartilage only and not bone with in the study used in vivo osteochondrogenic assay[45].

In another study, Karlsson et al[46] compared articular chondrocytes and iliac crest derived MSCs and allowed them to differentiate in so called pellet mass cultures. Significantly decreased expression of collagen type I was accompanied by increased expression of collagen types IIA and IIB during differentiation of chondrocytes, indicating differentiation towards a hyaline phenotype[46]. Chondrogenesis in MSCs on the other hand resulted in up-regulation of collagen types I, IIA, IIB, and X, demonstrating differentiation towards cartilage of a mixed phenotype[46]. These findings suggest that chondrocytes and MSCs differentiated and formed different subtypes of cartilage, the hyaline and a mixed cartilage phenotype, respectively[46] and the bone marrow stem cells are prone to produce bone instead of cartilage. Such a finding is important to know about as when surgeons are doing bone marrow stimulation like micro-fracturing (MFX) with a risk of too much bone ingrowth. Some factors that promote chondrogenesis while inhibiting hypertrophic changes from MSCs might be necessary for the cartilage engineering from non-chondrocyte MSCs.

THE FUTURE ACI

Combinations of chondrocytes and MSCs

New findings demonstrate that co-culturing human MSCs with human articular chondrocytes in HA-hydrogels enhances the mechanical properties and cartilage specific ECM content of tissue-engineered cartilage[47]. However, co-culture decrease the expression of collagen type X by MSCs, which is an important marker of MSC.

Initially, it was thought that when mixing chondrocytes with MSCs, the MSCs were recruited by the chondrocytes to go into a chondrogeneic lineage. Recent studies instead show that MSCs are functioning as medicinal signaling cells to stimulate the chondrocytes for a stronger repair response[7].

Subsequently when to repair a cartilage defects at least for larger defects, chondrocytes are needed in some form. With the complicated regulations regarding chondrocyte cultures, the possibility of using direct isolation of chondrocytes mixed with MScs as one-stage procedures has open new doors for cartilage repairs[21,22].

One-stage ACI techniques are called ACI 4th generation. In the INSTRUCT study, the surgeons harvested bone marrow cells from iliac crest and mixed them with chondrocytes directly isolated in the OR[21]. The cell mixture was then injected in a scaffold for a direct cartilage lesion implantation. In a 24 months study in 40 patients, good lesion fill and sustained clinically important and statistically significant improvement were found in all patient-reported outcome scores throughout the 24-month study. Hyaline-like cartilage was observed on biopsy specimen in at least 22 of the 40 patients[21].

Another such one-stage procedure is the IMPACT study[22] where instead of direct isolation of chondrocytes, chondrocytes with surrounding pericellular matrix is isolated as chondrons. The chondrons are then mixed with allogeneic MScs and injected in fibrin glue into the defect. Using allogenic MSCs, no signs of a foreign body response or serious adverse reactions were recorded after 5 years. The majority of patients showed statistically significant and clinically relevant improvement in the KOOS and all its subscales from baseline to 60 months[22].

Minced cartilage derived ACI

However, even if those above described techniques are one-stage procedures, they involve cell isolations through minor manipulations and cells with osteogenic potential that may influence the degree of chondrogenesis. A simpler, one-stage procedure is then to use particulated or fragmented cartilage for repair. The initial technique called CAIS was studied in two RCTS[23,48] showing in both studies significant improvement of the patients treated by cartilage fragments in resorbable scaffold versus microfracture. Unfortunately, the company developing CAIS decided not to launch the technique for further use commercially. Instead, other companies have used the technology to develop modified versions of CAIS with fragments in different scaffolds.

Williams and co-workers[49] have identified a population of chondroprogenitor cells

Image: Illustration.

from the surface zone of bovine articular cartilage using differential adhesion to fibronectin[49]. This population of cells can form large numbers of colonies from a low seeding density and is capable of extended culture without losing the chondrogenic phenotype and they are subsequently cartilage progenitor cells[49].

Therefore, these populations are expected to be extra interesting potential cell sources for cartilage repair as being cartilage pluripotent "stem cells". Migratory ability enables cartilage-derived pluripotent cells to migrate to the injured site and repair cartilage damage. Even stem cells from human OA cartilage also have the potential for cartilage repair. Koelling et al[50] observed that also cartilage progenitor cells from late stage OA knee joints regained a round chondrocyte-like phenotype and exhibited collagen type II mRNA expression as well as collagen type II protein expression in a 3D-alginate culture without any chondrogenic supplementation[50].

Based on such findings, the use of fragmented cartilage is of increasing interest as it has been shown in laboratory experiments that new cartilage tissue is formed in direct connection to the fragments. Endogenous cartilage progenitor cells migrate from the fragments into the surrounding scaffolding material to start new matrix production. With special harvest instruments mini fragments are produced which could be put onto different scaffolds and be implanted fixated with a biological glue[25].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Marmotti et al[51] have shown that there is an age-dependent and time-dependent chondrocyte migration. A significant difference ($P < 0.05$) was observed between young and older donors[51]. Furthermore, it has also been shown that at one month high cellularity and intense extracellular matrix (ECM) production could be seen and that a two months, ECM was positive for collagen type II[52]. Furthermore, the matrix production is influenced by the degree of fragmentation and Bonasia et al[53] found that a chondral paste of fragments with size < 0.3 mm performed best in histology comparisons[53].

Juvenile chondrocytes have shown in vitro superior capabilities of producing cartilage extracellular matrix [54]. With the knowledge of chondral fragments for cartilage repair, now also allogeneic juvenile cartilage fragments have been introduced for chondral repair[26,55].

3D-printing of chondrocytes in Bio-ink with Biopens

The concept of 3D-printing involves a construct production having a control over spatial resolution, shape, and mechanical properties[56]. When to repair a cartilage defect, a gradient repair is important where cells in different layers may be able to via cross-talking develop a good quality repair. Many of the 3D printing concepts involve several cell types and different materials for the bone and cartilage layer. Most often an osteochondral repair approach is best with a 3D printing addressing the bone defect with printing of bone cells into layers of bone substitute materials like hydroxyapatite and followed by different chondrocytes printed layered between a more cartilage specific matrix materials like hyaluronic acid[57,58].

The status of the Chondrocyte for cartilage repair in randomized controlled trials

Randomized controlled clinical trials (RCTs) are considered to be the gold standard for evidence-based medicine. Subsequently, RCTs are important in also cartilage repair methods, steering the surgeons to use well-controlled and validated methods. In 2019, Matar and Platt[59] published a paper on RCTs in orthopedic reseach[59]. The authors included 1078 RCTs across seven most commonly performed elective procedures. Unfortunately, cartilage repair procedures were not included in their review. Of the seven procedures studied, only 16% of the RCTs reported significant findings.

However, from 2003 to 2021, 21 RCTs have been performed[23,48,60-79]. Sixteen of those RCTs involved different generations of ACI versus other cartilage repair techniques[23,48,63-78]. In 9 of those 16 studies, ACI showed significant superiority in different parameters studied versus the other cartilage repair method[23,48,65,70-74,76]. Ten of those studies involved different generations of ACI versus bone marrow stimulation without scaffold (MFX (9) and abrasion arthroplasty (1)[23,48,68,69,70-74,76]. ACI was significantly better in different parameters than BMS without scaffold in 8/10 studies[23,48,70-74,76] (Figure 4).

How and when to use chondrocytes for a cartilage repair?

There are numerous algorithms to use for cartilage repair. Most often the surgeons trend to overestimate the size of the lesions to repair.

The mean size width of the both condyles in a man is a little less than 9 cm[90]. A defect with a size of 1 cm located centrally on a condyle is subsequently quite a large defect to repair.

The authors' suggestions of methods to use for a cartilage defect are:

- BMS (like MFX or drilling) for small defects 0.5 cm²
- Augmented BMS (with a scaffold) for small-medium sized defect 0.6-2 cm²
- Alternative also for re-operations in such defects if a simple BMS has been done before
- ACI-one stage with autologous or allogeneic chondral fragments >1cm²
- ACI-two stage with cultured chondrocytes > 2 cm²
- ACI-one stage with mixed chondrocytes and MSCs > 2 cm²
- Above Cell based treatments for re-operations > 1 cm²
- Osteochondral Allografts for extra-large defects like condylar replacements

It is also important not to forget that unloading osteotomies are useful in combination with local repairs.

Furthermore, as mentioned earlier in the text, the activities of chondrocytes are depending on the patients' age. A local cartilage repair can be done for local trauma defects, local degenerative lesions but may also be used for a local well-defined lesion in an early OA joint. However, local repairs are not used in a full established osteoarthritic joint.

Chang and co-workers[81] have detected multipotent mesenchymal progenitor cells in human articular cartilage of all ages. Of interest to know is that chondral progenitor cells accounted for 94.69%±2.31%, 4.85%±2.62%, and 6.33%±3.05% of cells in articular cartilage obtained from fetuses, adults, and elderly patients, respectively (P<.001)[81]. Furthermore, fetal mesenchymal progenitor cells had the highest rates of proliferation measured by cell doubling times and chondrogenic differentiation as compared to those from adult and elderly patients[81]. With that in mind, the repair quality is expected to become better, the younger patient that is treated but ACI may be used in elderly patients still having in total a healthy cartilage as there also exist cartilage progenitor cells but with less chondrogeneic differentiation ability.

Third Party Testing

ACI Gen I versus Gen II and III
= *Schneider et al 2003*
= *Bartlett et al*
= *Gooding et al*
= *Zeifang et al 2010*

ACI Gen I versus Mosaicplasty
= *Horas et al 2003*
+ *Bentley et al 2003*
= *Dozin et al 2005*

ACI Gen III versus Mosaicplasty
- *Clavé et al 2016*

ACI Gen I versus MFX
= *Knutsen et al 2004*
= *Lim et al 2012*
+ *Vanlauwe et al 2011*

ACI Gen III versus MFX / Abrasion Arthroplasty
+ *Visina et al 2004*
+ *Basad et al 2010*
+ *Crawford et al 2012*
+ *Saris et al 2014*
+ *Niemeyer et al 2019*

ACI Gen II versus AMIC (Scaffold + bone marrow stimulation)
= *Fossum et al 2019*

ACI Gen III versus AMIC (Scaffold + bone marrow stimulation)
- *Akgun et al 2015*

ACI Gen III with scaffold free ACI in comparison to three different cell concentrations
= *Becher et al 2017*

ACI Gen IV versus MFX
+ *Cole et al 2011*
+ *Spalding et al 2011*

Figure 4: A summary of the RCTs done with ACI versus different other methods from 2003-2021.

> ***The chondrocytes are the masters of the cartilaginous tissue and they are subsequently still most valuable to use when to repair a traumatized cartilage.***

CONCLUSION

The chondrocytes are the masters of the cartilaginous tissue and they are subsequently still most valuable to use when to repair a traumatized cartilage. DNA methylation is essential for normal development and is associated with a number of key processes[82]. Besides what has been mentioned about the strong chondrogeneic ability of primary chondrocytes compared to MSCs of different origins, Bomer et al[82] have nicely shown that In vitro engineered neo-cartilage tissue from primary chondrocytes exhibits a DNA methylation landscape that is almost identical (99% similarity) to autologous cartilage, in contrast to neocartilage engineered from bone marrow-derived mesenchymal stem cells (MSCs).

I still believe that we will use chondrocytes for a biological repair in the future but with fewer manipulations of the cells due to the strict regulations world-wide making cell expansion and culture expensive. Different variants of one-stage procedure will appear more and more with both autologous or allogeneic cells and even mixtures. The dream goal is a full cartilage regeneration still not achieved in a clinical setting. However, when to reach as near as possible regeneration, true committed chondrocytes and chondral progenitor cells seem still to be the best choice in 2021.

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ADIPOSE TISSUE

AN AMAZING SCAFFOLD FOR ONE-STEP BIOLOGICAL CARTILAGE REPAIR

– Written by Fabio Valerio Sciarretta, Italy

INTRODUCTION

Articular cartilage is avascular, aneural, alymphatic and has limited capacity for intrinsic repair or regeneration.

Over the last decades scientists have proposed several treatment options for the treatment of focal cartilage defects. For smaller cartilage lesions, these modalities include debridement, marrow stimulation through microfracture, abrasion, drilling and nano-fracture, advanced scaffold augmented marrow stimulation techniques (AMIC, BST-Cargel, GelrinC)), and osteochondral autograft transplantation (OATS) / mosaicplasty. For larger lesions, osteochondral allograft transplantation and autologous chondrocyte transplantation (ACI) have been introduced and appear to be highly effective.

The goal of any cartilage restoration procedure is to restore the articular surface by matching the histological, biochemical, and biomechanical properties of normal hyaline cartilage, improve patient symptoms and function, and prevent or at least slow down the progression of focal cartilage injuries to end-stage arthritis.

In an attempt to repair or regenerate articular cartilage in more recent years orthobiologic treatments with cells, mesenchymal stem cells (MSCs) and growth factors have become a new major interesting treatment choice for different pathologies regarding muscles, tendons, bone and especially cartilage.

MSCs are certainly the most investigated and used cell type and play a crucial role in most of the possible application protocols. Most recent discoveries have demonstrated that MSCs derive from perivascular cells named as "pericytes", located in the proximity of blood vessels[1,2]. Pericytes belong to the so called "perivascular niche"[3], where they live in a quiescent condition. When a vessel is damaged, as normally occurs during an injury, this event leads to the release of pericytes that from a quiescent phase pass to an activated phase, finally acquiring a MSCs phenotype. Activated MSCs start to release a cascade of bioactive molecules to counteract the overaggressive immune response[5] and trophic factors to establishing a regenerative microenvironment, promoting angiogenesis and stimulating proliferation of tissue specific progenitor cells[4,5].

The updated interpretation on MSCs activity, emphasises the fact that these cells show a very effective in vivo function and attributes their therapeutic action mostly to the demonstrated important paracrine and trophic actions that these cells are able to carry out. For this reason, MSCs have been recently defined as a "drugstore", since their ability to release a wide range of growth factors and cytokines in the surrounding microenvironment actually mimic the effect of a very powerful drug administered locally[5,6].

Orthobiologics include bone marrow aspirate concentrate (BMAC), Adipose Tissue-Derived Stroma Cells (ADSCs), platelet-rich plasma (PRP) and micronized allogeneic cartilage. Parallel to the use of orthobiologics, another promising strategy that has been recently introduced and extensively studied is the use of scaffolds alone or of scaffolds seeded with MSCs to enhance their differentiation in chondrocytes and form hyaline cartilage. In fact, if from one side scientists in the last years have been focusing on improving scaffold-based ACI, the literature[7] has seen and confirmed a constantly growing interest in looking for different solutions to regenerate the damaged articular cartilage by the use of different MSCs sources as a new powerful tool for three-dimensional scaffold augmentation surgical regeneration techniques.

Clinical applications of MSCs should meet the minimal criteria established by International Society for Cellular Therapy including[8] being plastic-adherent in culture conditions; expressing cluster of differentiation 105 (CD105), CD73, and CD90, lacking expression of CD45, CD34, CD14 or

CD11b, CD79 or CD19, and human leukocyte antigen-DR isotype (HLA-DR) surface molecules; and (3) possessing tri-lineage differentiation into osteoblasts, adipocytes and chondroblasts.

In Orthobiology, the innovative field of modern biomedical technology that provides biologic therapies for reconstructing damaged tissues, the utilised mesenchymal stem cells are in most cases obtained from bone marrow or adipose tissue.

In the past decade, adipose tissue has become a highly interesting source of adult stem cells for plastic surgery and regenerative medicine. More recently adipose tissue, that is provided of a consistent vasculature, has been progressively recognized as a smart source of these cells that can be easily collected in abundance with a lower invasiveness for the patient and fewer age-related restrictions. Adipose tissue grafts and ADSCs can be isolated from the upper arm, medial thigh, buttocks, trochanteric region, superficial deep abdominal depots and infrapatellar fat pad.

Subcutaneous adipose tissue is up today the first choice for cell isolation because it is easily accessible via liposuction, is relatively abundant in many patients, can be harvested by a minimally invasive procedure and can be safely and effectively transplanted to either in autologous or allogeneic setting[9-11]. This type of tissue provides an abundant source of stromal vascular fraction (SVF) cells for immediate administration.

The SVF fraction contains multiple non-cultured cell types, including preadipocytes, mesenchymal (MSCs) and endothelial progenitor cells (EPCs), fibroblasts, pericytes, and vascular smooth muscle cells. There are varieties of isolation systems commercially available for SVF isolation assuring a reproducible and consistent composition of heterogeneous cells[11-14]. Upon processing and administration, the adipose-derived SVF cells can differentiate into different tissue types, support neovascularization, replace cells and repair injured tissue.

Each adipocyte is completely surrounded by a capillary system, thus explaining how the amount of MSCs in adipose tissue is five time higher than the bone marrow's one. The identification of the stroma and the possibility to use this stromal vascular fraction with its high prevalence of stem/stromal cells for therapeutic uses, has made, as said, the adipose tissue a suitable source for clinical applications.

Image: Illustration.

Adipose tissue contains, in fact, a great number of stem cells (ADSCs), 500-fold greater than BM-MSCs. ADSCs represent a population of adult MSCs able to self-renew and multipotentially differentiate into adipocytes, chondrocytes, myocytes, osteoblasts, and play a key role in reconstructive or tissue engineering medicine, alone or in combination with biomaterials, growth factors or different types of scaffolds. According to published studies, cartilage repair with scaffold augmentation has improved clinical outcomes, radiological fill, and histological repair compared with microfracture alone. In particular, already in 2017, Pot et al[15] in a systematic review and meta-analysis on cellular and cellular scaffolds concluded that cartilage regeneration using ADSCs-seeded scaffolds improved regeneration compared to acellular scaffolds.

Collagen is one of the major components of cartilage ECM, and collagen-based scaffolds have been proven capable of retaining MSCs, providing high biocompatibility and a chondrogenic environment thus supporting functional cartilage regeneration. In particular collagen materials have been proven to provide a proper environment for cell invasion, facilitating cell colonisation through the pores of the material and finally enhancing chondrocytes differentiation. Thus, MSCs present in collagen scaffolds can maintain a chondrocyte phenotype in chondrogenic culture conditions and produce new collagen.

Cartilage defects repair by ADSCs has begun after that, in 2001 and 2002, Zuk et al[9,10] have been able to identify the processed lipoaspirates cells (PLA) and confirmed their ability, like MSCs, to differentiate toward chondrogenic lineages. The authors, in fact, proved that PLA cells were able to express a unique set of CD markers, could synthetize cartilaginous matrix and express chondrogenic lineage genes.

Cell separation with minimal manipulation exploits mechanical steps, such as centrifugation, pressure, filtration and micro-fragmentation to separate cells from adipose tissue. Different closed systems based on these minimal manipulation technologies have been developed to harvest, concentrate and transfer the patient's own adipose tissue in the clinical setting meeting the strict regulations on MSCs use[16-21].

Nowadays, the literature has confirmed the good results obtained with ADSCs both as intra-articular injections in the hip and the knee as OA treatment and as orthobiologic complex scaffold reconstruction surgeries.

We personally developed the so-called LIPO-AMIC procedure[22], where the cartilage defect is, in the same operating procedure, subjected to careful debridement, accurate microfractures and finally collagen membrane coverage arthroplasty, where the especially studied 3Dmatrix bi-layer scaffold is carefully cut to the same size and shape of the defect to be treated and soaked for 10-15 minutes in the micro-fragmented adipose tissue transfer graft containing ADSCs and the stromal vascular fraction. To obtain the adipose tissue graft, a small quantity of lipoaspirate (about 50-80 ml), obtained from the abdomen adipose tissue reservoir, is treated in a closed system through a dedicated single-use kit available on the market for suction and subsequent processing (filtration and micro-fragmentation) and adipose tissue grafting, based on the mechanical disruption of the sample that enables to discard oil and debris and maintain cells niche and secretome and forward the graft in a syringe ready for use.

The LIPO-AMIC technique has been used for the treatment of knee symptomatic degree III and IV focal cartilage defects according to the classification of the International Cartilage Regeneration and Joint Preservation Society (ICRS) greater than 1 cm² in size (mean lesion size, 3,1 cm²) and affecting the femoral condyles, medial or lateral, or the retrosurface of the patella or the femoral trochlea.

DETAILS OF SURGICAL TECHNIQUE

The patient undergoes one-step biological resurfacing procedure using microfractures, adipose tissue graft, ADSCs and collagen

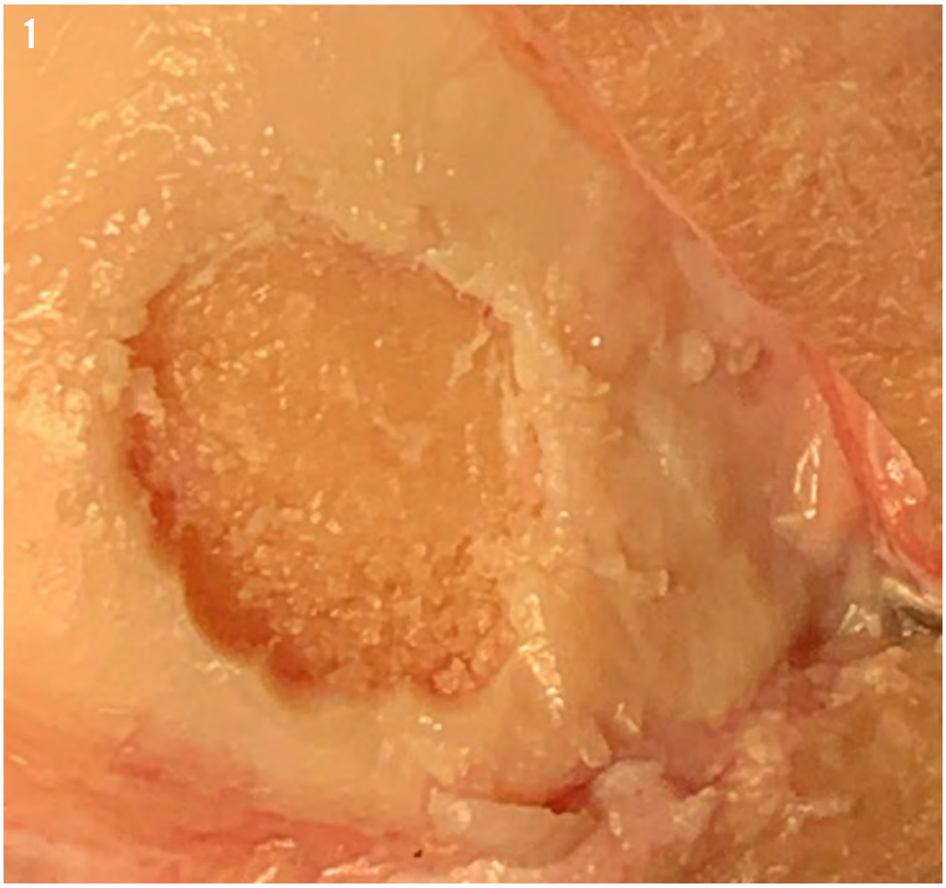

Figure 1: Large full thickness osteochondral defect of the articular surface of the patella.

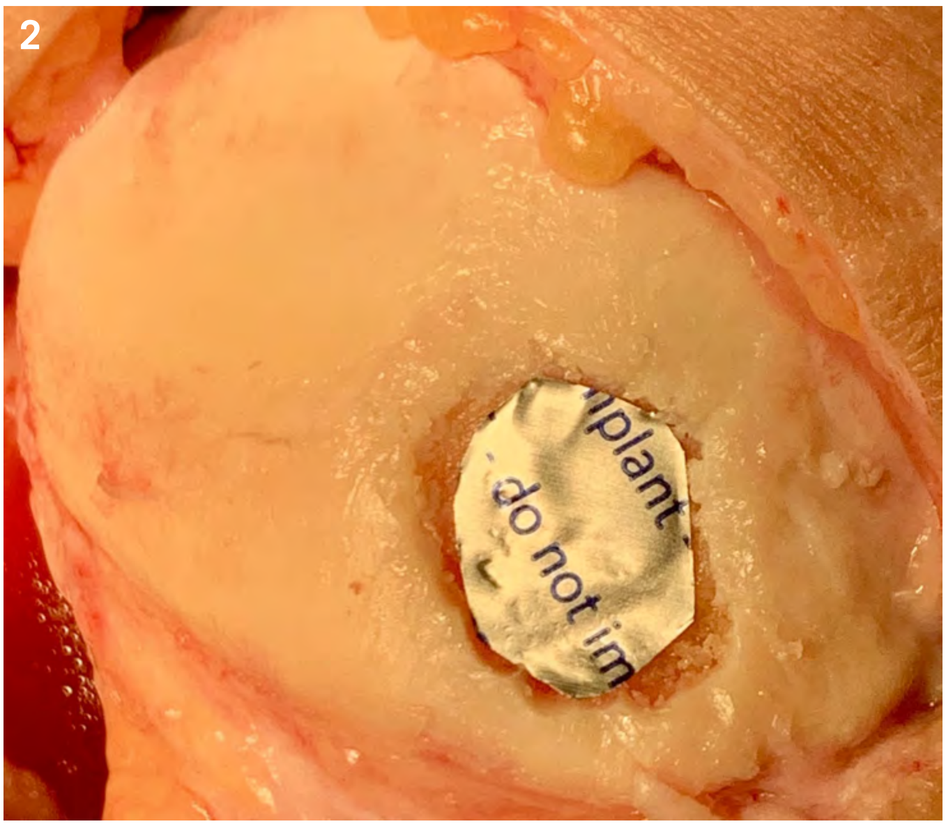

Figure 2: Creation of an exact figure of the full thickness osteochondral defect through the sterile aluminium template provided in the collagen membrane kit that will be used for the repair.

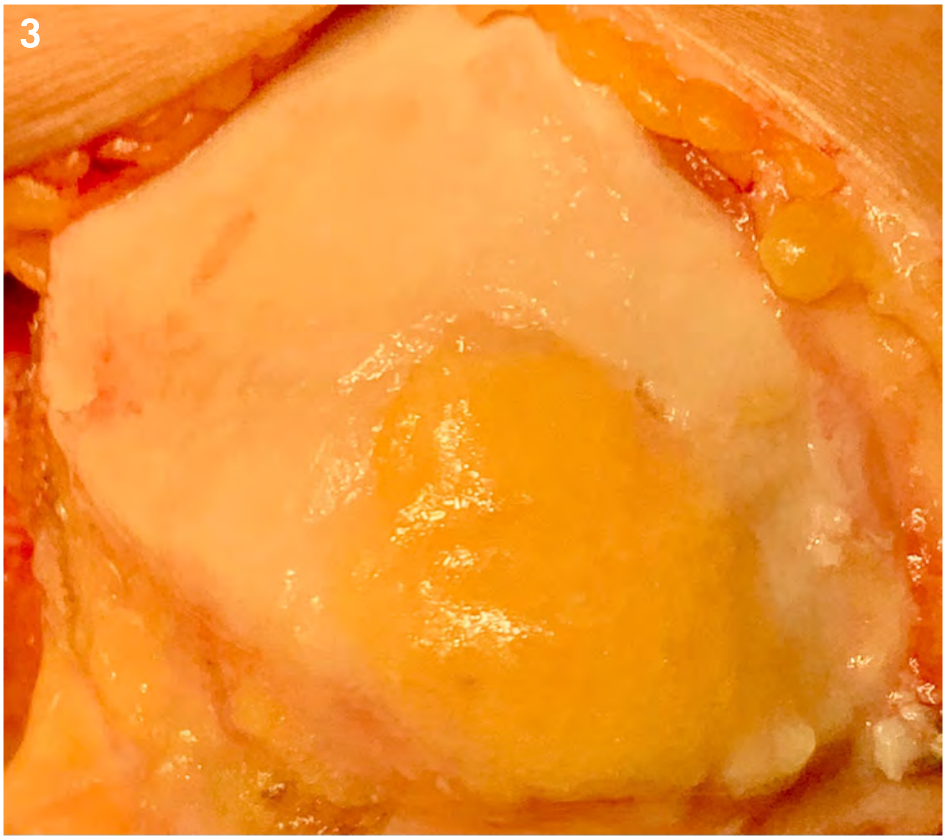

Figure 3: Biologic resurfacing arthroplasty of full thickness osteochondral defect of the articular surface of the patella by collagen membrane augmented with adipose tissue graft and ADSCs withdrawn form subcutaneous adipose tissue of the abdomen.

membrane coverage of full-thickness defect following arthroscopic confirmation of the presence of a defect suitable for such treatment (Figure 1).

All surgical procedures are performed in a single surgical step, under loco-regional anesthesia and after routine preparation of the sterile operating field.

The first phase of the procedure involves performing a normal diagnostic arthroscopic examination through the anteromedial and antero-lateral standard portals to confirm magnetic resonance imaging findings with respect to location and size of the lesions. During this phase, all the compartments of the knee are inspected, including the suprapatellar pouch, the medial and the lateral gutters, the patellofemoral joint, the intercondylar notch and the central pivot, the medial and lateral compartments, with particular probing and rating of the cartilage lining of the femoral condyles and the posterior horns of the medial and lateral menisci. Completed the diagnostic stage, which also ensures the site, the extent and depth of the chondral or osteochondral defect, the associated meniscal or synovial pathologies are treated during the standard arthroscopic surgical procedure.

Subsequently, under local anesthesia of the abdomen, after infiltration of Klein's solution, 50-80 ml of lipoaspirate are extracted by the simple method of lipoaspiration from the periumbilical adipose tissue, using the Lipogems® dedicated disposable kit available on the market for the suction and subsequent processing (filtration and micro-fragmentation) and grafting of adipose tissue, for the use of which we follow the instructions provided by the manufacturer. This device progressively reduces the size of the adipose tissue clusters, at the same time eliminating blood residues and oily substances with pro-inflammatory capacities, minimizing, thanks to the carrying out of the whole process inside physiological solution, the risks of damaging the mesenchymal stem cells.

Once the adipose graft harvesting process has been completed, the following step of the surgery is the repair of the focal chondral or osteochondral defect. Identified the full thickness cartilage defect, a thorough and extensive debridement of the defect is completed. At this stage, it is extremely important to focus in removing all the damaged and / or unstable cartilage till reaching the surrounding healthy cartilage tissue, creating solid and net margins. For this manouver, generally, straight or curve curettes, specific designed chondrotomes and an arthroscopic full radius cutter are used to carefully remove the cartilage degenerated or only partially still connected at the defect's edges. It is important to take care to remove always the calcified cartilage layer with a curette, also taking the utmost care in not to trespassing the subchondral plate.

Once completed the debridement and the careful grooming of the cartilage defect, the defect is measured and an exact figure is created through the sterile aluminum template provided in the collagen membrane kit that will be used for the repair of the full thickness cartilage defect (Figure 2). Thus, the exact imprint of the defect is cut out. Always remember to identify the side of the template, and then of the membrane, which will be placed in contact with the defect, in order to avoid obtaining a membrane of the wrong shape to apply on the defect. This same template will then used to prepare the scaffold used for the biological resurfacing.

While the cut membrane is soaked in the adipose tissue graft, we perform the microfractures in the subchondral bed of the lesion, using different angled drills, until reaching the subchondral bone. The microfractures are performed starting from the periphery of the defect proceeding concentrically toward the center of the defect itself, keeping a distance of 3-4 mm. between a perforation and the other and placing the utmost care in avoiding the convergence of a perforation in the other. Once reached the appropriate depth, typically 2-4 mm., leaking of some droplets of blood or fat is seen, which confirms the proper execution of the technique. After finishing the microfractures and verified to have penetrated the entire defect, it is important to carefully remove all the produced debris.

Completed the microfractures, the Chondro-Gide® collagen bilayer membrane is cut so that it has exactly the size and shape of the shape previously prepared. Once cut, the dry membrane is laid on the defect in order to make sure the size is perfect, even in anticipation of the increase in volume of the membrane (10% -15%) as a result of its impregnation with the adipose tissue graft. This scaffold is a double layer membrane with a smooth side, waterproof and capable of retaining the cells, and the other wrinkled and porous.

Next step is the repair of the defect. This phase involves several sequential steps: first step is the injection of ADSCs in the defect bed. Then the enriched membrane is inserted into the joint to directly and accurately cover the defect. It is therefore crucial to be sure to apply the cell adhesive porous layer of the scaffold towards the bed of the defect in order to correctly favour cell entrapment.

The remaining part of the cells obtained from the adipose tissue is infiltrated on the site of the lesion and then, membrane and adipose graft and MSCs are sealed and secured to surrounding cartilage by use of fibrin glue (Figure 3).

The collagen membrane constitutes an ideal scaffold as its porous nature allows the cells to nest inside the cells, thus finding the most suitable environment for growth and differentiation. In this way, the membrane will perform a double action: in addition to representing the barrier capable of retaining the mesenchymal cells from the medullary blood, it constitutes a scaffold enriched and activated by the mesenchymal adipose cells to accelerate the process of chondrocyte development and differentiation.

After complete adhesion of the scaffold, the joint is several times completely flexed and extended and the stability of the applied membrane is checked. Completed the surgical procedure, a compression bandage is applied.

POST-OP PROTOCOL

The postoperative protocol foresees the progressive immediate partial loading assisted by crutches. In the first post-operative day, the patient starts immediately to regain joint ROM. The careful evaluation of the compliance characteristics of each patient argues in favor or not to use the passive joint mobilization (CPM), which allow to promote cartilage healing by favoring joint nutrition and reducing intra-articular adhesions formation. Range of motion and weightbearing protocols are differentiated depending on defect location, on the femoral condyle or the patello-femoral joint. In case of patello-femoral joint defects, progressive weightbearing with crutches is immediately allowed, limiting ROM from 0 degrees to 60 degrees of flexion for the first 3 weeks. In femoral condyles defects, weight bearing is restricted for the initial four weeks postoperatively, achieving unrestricted complete weightbearing generally by six weeks. Great importance is emphasised on early regaining of normal gait patterns. Once muscle strengthening is completed and joint movement is fully recovered, specific sport activity exercises are initiated under strict guidance of physiotherapist and trainer.

RESULTS

All patients with chondral injuries treated with the LIPO-AMIC technique have been followed prospectively and have been evaluated both clinically and by magnetic resonance imaging with progressive follow-ups at 6 and 12 months and have been available for follow-up assessments at 2 and 5 years postoperatively.

The clinical, and MRI follow-ups at 2 and 5 years have confirmed the good results with repair and regrowth of the cartilaginous tissue able to gain complete filling of the defects.

Evaluation of MR images progressively showed in the follow-up controls a significant reduction in the area of the chondral defect, with complete filling of the defect in the majority of cases, in the absence of signs of hypertrophy or bone oedema.

Parallel to the clinical study, we have also conducted an analysis of the fresh ADSCs isolated from adipose tissue lipoaspirate samples withdrawn to evaluate their biologics, integrity and viability to confirm their ability to guarantee safe and effective repair of articular cartilage defects. SVF cellular components from untreated lipoaspirate samples have been compared with corresponding cells deriving from lipoaspirate samples processed by micro-fragmentation, to evaluate cell composition, and preservation of viability. The outputs were characterized using multicolor Flow Cytometry (FC) analysis. We have found a consistent increase in the percentage of endothelial cells and pericytes in the processed samples by micro-fragmentation system compared to lipoaspirate untreated samples thus confirming that the mechanical withdrawal procedures may maintain a large cell population heterogeneity, preserving the niche tissue architecture.

CONCLUSIONS

In last years the literature has seen the publication of several phase I, II and now also III ADSCs trials that have confirmed the optimization of ADSCs preparations, good clinical results and safety of the procedures injecting or transplanting ADSCs using various scaffolds.

ADSCs implantation obtained by the single-step LIPO-AMIC procedure has provided encouraging outcomes with acceptable and more durable duration of symptom relief at midterm follow-up at 2 and 5-year years, thus representing a possible alternative to standard autologous chondrocyte implantation at lesser costs.

Cartilage regeneration by scaffold augmented techniques is nowadays a reality that holds significative promise for improving the results of cartilage repair and promoting the must of joint preservation, looking forward in the future to refine more and more increasingly mini-invasive and arthroscopic implantation techniques that together with novel next-generation biologics addition may improve the quality of tissue repair and faster the repair tissue integration and maturation processes.

Orthopaedic surgeons must, therefore, believe and get experienced in cartilage repair in order to fight joint degradation and OA development and keep patients on their legs to continue all daily and sport activities and move away the spectrum of a total joint procedure.

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ONE-STAGE CELL THERAPIES – STATE OF THE ART TECHNIQUE

– Written by Konrad Słynarski, Poland , Theodorakys Marín Fermín, Venezuela and Emmanouil Papakostas, Qatar

INTRODUCING THE VILLAINS

Epidemiology of Cartilage Injuries

Cartilage injuries are potentially harmful lesions affecting around 60% of patients undergoing knee arthroscopy[1,2]. Full-thickness focal defects are more frequently found in athletes and may be present in up to 59% of them[3,4]. The most common locations are the patellar (36%) and medial femoral condyle (34%) surfaces and are often associated with a medial meniscus tear (42%) or anterior cruciate ligament injury (36%)[1]. While most isolated chondral injuries are asymptomatic, they may present with pain, locking or catching sensation, swelling and/or pseudoinstability[4].

Cartilage Healing Potential

Due to the highly specialized hyaline cartilage cells and tissue properties, its regeneration potential is low[5]. Additionally, the avascular nature of cartilage tissue and incapacity for clot formation hinders the main steps that occur in other tissues after an injury[6,7].

Cartilage tissue attempt at healing depends on defect size and depth[8]. Partial-thickness cartilage injuries do not violate the subchondral bone and do not repair spontaneously[5]. Cell adjacent to the defect margins undergoes cell death, and chondrocytes and migrating synovial cells fail to fill the defect after an injury[5,9,10].

On the other hand, the healing process after full-thickness injuries involves several cell types arising from the bone marrow after subchondral plate breaching[11]. In these cases, the resulting synthesized extracellular matrix after hematoma formation does not replicate the native morphology and mechanical characteristics of the native tissue but produces fibrocartilage[5]. This fibrocartilage tissue primarily consists of collagen I fibers with limited durability[12].

Furthermore, smaller lesions may dissipate weight-bearing forces across it, protecting the subchondral bone, but larger lesions may fail to do so. In those cases, the exposed subchondral bone will become abrasive to the opposite chondral surface, creating bipolar injuries and consequent subchondral edema[7,13]. When untreated, these defects may progress to knee osteoarthritis[5,14].

Several treatment approaches are available to address focal cartilage injuries of the knee. However, the standard treatment is yet to be defined. Non-surgical options include rehabilitation and physical therapy, and intra-articular injections[15]. On the other hand, surgical treatment options range from debridement and bone-marrow stimulation techniques to more complex procedures, including osteochondral autologous transplantation, osteochondral allografts, mosaicplasty, and cell-based therapies[16].

Costs of Autologous Chondrocyte Implantation (ACI)

Knee ACI, first performed in 1994, showed promising results in managing focal cartilage injuries[17]. Studies have addressed its cost-effectiveness with favorable results, with cost savings related to fewer work absences and disability[18]. This is especially relevant in the young and active population, in which regenerative techniques potentially allow better and sustained long-term outcomes compared to other techniques[19].

Everhart et al[18], in their systematic review, found that matrix-induced autologous chondrocyte implantation

Image: Ilustration.

(MACI) had better cost-efficacy than its counterpart implementing a periosteal cover, with costs surpassing 50,000 USD per quality-adjusted life-year over ten years. However, this two-stage procedure is still expensive, costing approximately 16,226 EUR[20]. The need for a second procedure is a difficulty that translates into additional indirect costs from loss of productivity and qualitative deleterious effects from a time and monetary point of view[18].

Likewise, Its logistical complexity and the need for chondrocyte culture in highly specialized laboratories with processing costs exceeding 30,000 USD in the United States have limited its widespread implementation[21,22]. Since then, numerous modifications of this technique have been introduced, aiming for a single-stage definitive solution given its cost-saving potential.

CHOOSING THE WEAPONS

Chondrocytes: The Secluded Cell of Cartilage Tissue

Chondrocytes are mesenchymal cells specialized in extracellular matrix synthesis[5]. They represent only 2% of the articular cartilage volume and lead the cartilage homeostasis through secreting enzymes, growth factors, and inflammatory mediators[5,7]. Cartilage extracellular matrix is mainly composed of collagen II fibers, proteoglycans, and glycoproteins. The matrix interweaved architecture results in unique viscoelastic properties, providing a smooth and lubricated surface for low friction movement and load transmission[5].

Chondrocytes are the only cells capable of creating new hyaline cartilage. Thus, the quest for cartilage restoration has involved its implementation in several attempts. ACI has been demonstrated to be an effective treatment option in managing large, full-thickness symptomatic chondral lesions of the femoral condyles with early improvement and sustained at long-term follow-up[23,24].

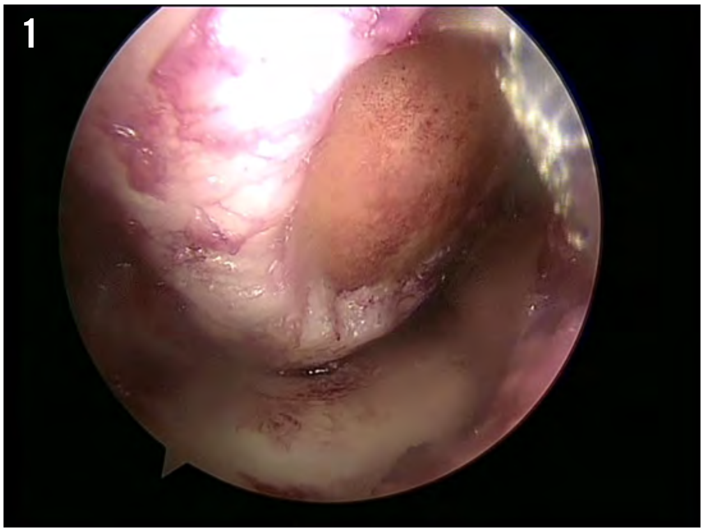
Moseley et al[23], in a multicenter observational study comprising 72 patients, reported that 75% of them improved from their baseline scores at 1 to 5-year follow-up, and 87% maintained their improvement to the last follow-up (mean 9.2 years), with an early failure rate in 17% of patients (mean 2.5 years). Similarly, Peterson et al[24] have reported similar outcomes in 224 patients with follow-up as long as 20 years.

While first-generation ACI has demonstrated satisfactory outcomes, there is still a gap for improvement in clinical outcomes, failure rates, and costs. Current practices aim to harvest chondrocytes from non-weight-bearing cartilage zones and implement fast isolation protocols, avoiding cell culture and two-stage procedures[25]. Moreover, it has been suggested that implementing chondrocytes from the injury rim or even arthritic cartilage seems not to alter the quality of newly synthesized cartilage, which may help to avoid donor-site morbidity[22,25].

Hyaline cartilage is harvested using a shaver or curettes from the medial margin of the medial femoral condyle, medial margin of the trochlea, or the lesion rim area to obtain approximately 0.3 g[25]. This tissue is recycled using enzymatic reactions to obtain chondrons (chondrocytes with their pericellular matrix) within an hour, enabling one-stage procedures. Cells are washed and counted to meet the density and ratio according to the defect[17,25].

Bone-Marrow-Derived Mesenchymal Stem Cells (BM-MSC): The Most Popular Stem Cell

Mesenchymal stem cells (MSC) are an adult lineage of multipotent cells with the potential to differentiate to the bone, cartilage, and other connective tissues by local signaling and genetic potential at embryonic stage[26,27]. However, according to the current understanding all MSC are pericytes, embeded in the capillaries, and



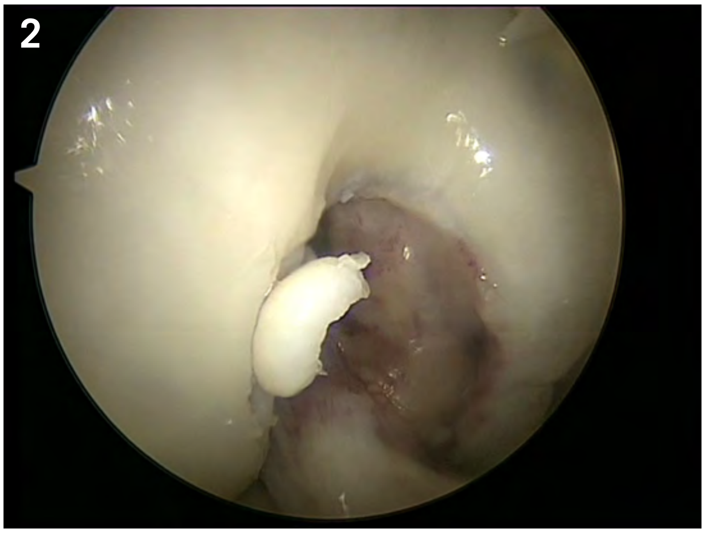


Figure 1: Cartilage defect of MFC after debridement and creation of stable shoulders.

Figure 2: Harvesting of healthy piece of cartilage from non-weight bearing area (notch).

Figure 3: Harvesting cartilage pieces from the defect.

Figure 4: Cartilage pieces minced and enzymatically digested to chondrons in the In-Theater portable lab.

do not differentiate to other cells type, but, when activated, secret growth factors that have influence on surrounding cell types[28].

Pericytes are stimulated by soluble growth factors and chemokines to become activated MSC, which respond to the microenvironment by secreting trophic (mitogenic, angiogenic, anti-apoptotic or scar reduction), immunomodulatory or antimicrobial factors[28].

They are currently the most widely used stem cells[29]. According to the International Society for Cellular Therapy criteria[30], a MSC must be (a) plastic adherent, (b) express CD105, CD73, and CD90, and not CD45, CD34, CD14, or CD11b, CD79 alpha or CD19, and HLA-DR surface molecules, and (c) differentiate into osteoblasts, adipocytes, and chondroblasts in vitro.

These cells are typically harvested in the iliac crest by aspiration, although the number of collected cells is minimal[31,32]. In the bone marrow of skeletally mature patients, the number of MSC ranges from 1:50000 to 1:100000, a few hundred per milliliter of marrow aspirate[31]. Furthermore, the implementation of allogeneic MSC has shown not to activate an adverse immune response while promoting chondrogenic potential of the surrounding chondrocytes, presenting as a safe option to be implemented.

Theoretically, the chondrogenic and trophic potential of MSC and homing are the most critical mechanisms in which these cells participate in the restoration of cartilage[27,33-35]. The first one, in which the cells differentiate to cartilage cells restoring the lost function and morphology; and the second, secreting several bioactive factors to promote repair environment[31]. The latter being the most accepted after de Windt et al[17] revealed that tracking these cells showed a temporary behavior, enhancing joint homeostasis before disappearing.

In a case series by Gobbi et al[21], successful comparable long-term outcomes in IKDC, KOOS, and Tegner activity scale were obtained when implementing BM-MSC in a hyaluronan-based scaffold for the treatment of full-thickness cartilage injuries ≥ 1 cm^2. The implementation of BM-MSC in a hyaluronan-based scaffold is an emerging therapeutic option among one-stage cartilage restorative procedures.

Synergistic Effect of Combined Chondrocyte and Mesenchymal Stem Cells

It has been suggested that a combination of chondrocytes and BM-MSC may increase the chondrogenic potential of the firsts[36,37]. Although MSC have shown no differentiation into chondrocytes in these circumstances in recent investigations[17], paracrine trophic and immunomodulatory effects contribute to the regeneration of the lesion[25]. It seems that MSC fade over time but secreting site-specific factors that promote tissue regeneration[17]. Complementing chondrocytes with MSC ensures a higher cell density in the defect and stimulates further hyaline matrix synthesis[25,38-41].

Scaffolds and Carriers

The use of scaffolds has also been widely studied during the last decades. They show advantages such as the uniform distribution of the seeded cells, provide a temporary platform for the new to be synthesized extracellular matrix which components may be implemented for such role[42-44].

Hyaluronan-based scaffolds and fibrin glue are among the most popular options, but new biomaterial are being continuously developed and studied for cartilage restoration[29,45-47]. To date, hyaluronan-based scaffolds have shown to be superior to other types, as they "recrerate" or mimic embryonic environment in limb buds development.

THE AVENGER

Indications

One-stage cartilage restoration with chondrocytes and MSC is the preferred technique for focal cartilage lesions on the femoral condyles or trochlear, ICRS II or III, > 1 cm², in adult patients with stable and well-aligned knees and meniscal loss < 50%[22,25].

One-Stage Restoration with Chondrocytes and Bone Marrow-Derived Mesenchymal Stem Cells: Surgical Technique[22,25]

Surgery can be performed via arthroscopy or a mini-arthrotomy approach. Cartilage defects are

debrided with curettes, removing the calcified layer and creating vertical and stable margins (Figure 1).

Cartilage pieces and BM-MSC are harvested afterward (Figures 2 and 3). Autologous chondrons (after enzymatic digestion of the minced cartilage) and MSCs are combined in a 1:9 ratio (standard) or 2:8 ratio (high yield) (Figures 4 and 5), depending on the number of isolated chondrons[17].

The lesion is measured, and a scaffold is prepared to meet the shape and thickness of the defect when implemented. In the next step the scaffold is implanted in the defect seeded with the cell mixture and further stabilized with the use of fibrin glue (Figures 6 and 7). Seeding after the fixation of the scaffold results in less cellular death resulting from manipulation[36]. The implantation of the cell mixture is also feasible directly in the fibrin glue without a scaffold.

Finally, the knee is tested for passive range of motion, checking the implant stability.

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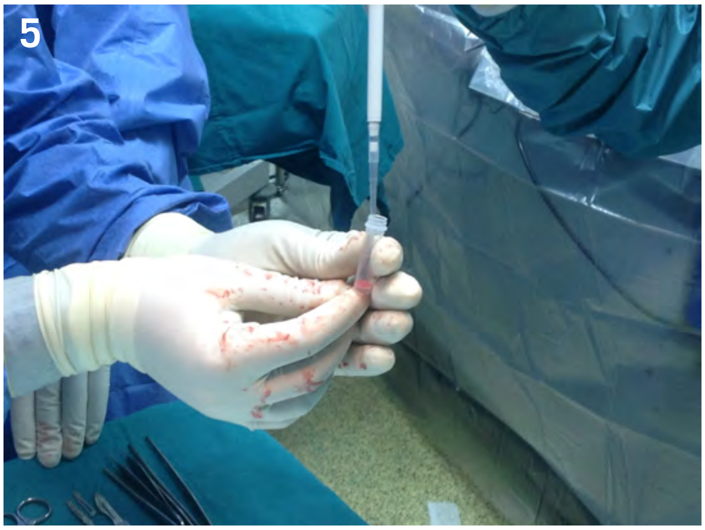

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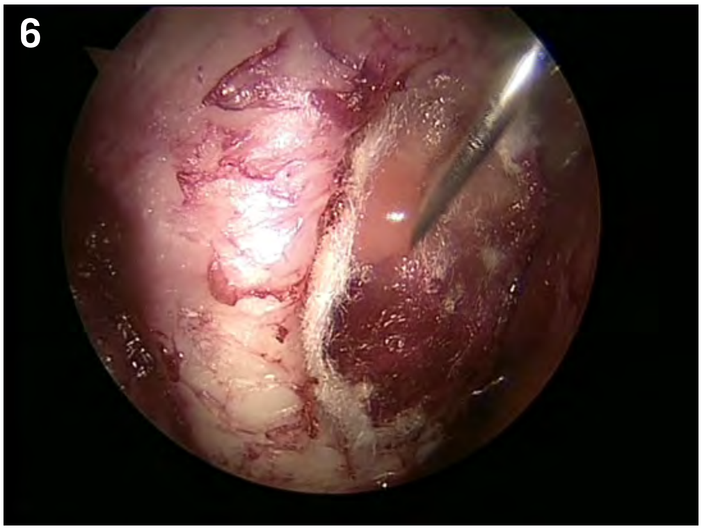

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Figure 5: Dilution of Chondrons and MSCs provided for final implantation.

Figure 6: Properly sized scaffold implanted and seeded with the dilution.

Figure 7: Fibrin glue used for final stabilization of the implant.

One-stage cartilage restoration using chondrocytes and MSC has proved to be a safe and reproducible technique, improving clinical outcomes and tissue quality of its predecessor two-stage ACI at two-year follow-up[17,25].

Outcomes: The Promise of a Definite Solution
One-stage cartilage restoration using chondrocytes and MSC has proved to be a safe and reproducible technique, improving clinical outcomes and tissue quality of its predecessor two-stage ACI at two-year follow-up[17,25].

Similarly, de Windt et al[17] implemented a combination of recycled chondrons from the lesion rim and cryopreserved allogeneic BM-MSC suspended in fibrin glue in 35 patients with full-thickness cartilage injuries with a mean size of 3.2 cm² ± 0.7, in a first-in-man clinical trial. Patient-reported clinical outcomes KOOS and VAS significantly improved from baseline scores up at 18 months after surgery, with the most considerable improvement at 3-month follow-up. Moreover, biochemical MRI, second-look arthroscopies, and histologic evaluation revealed a similar or higher quality in the new cartilage than in that obtained after ACI at 12 months. Hyaline-like cartilage was confirmed in almost 95% of the patients.

At a 5-year follow-up, the same patient cohort maintained the clinical benefits along with the follow-up, with fluctuations around the second year, probably related to the return to sporting activities. No serious adverse effects were recorded, and five patients required reintervention[22].

Similarly, in a prospective multicenter study using a combination of primary chondrocytes and bone marrow mononucleated cells in a hyaluronan-based scaffold, Slynarski et al[25] reported successful lesion filling in all 40 patients with ICRS II and III chondral lesions ≤ 2.6 cm² at 3-month follow up and in all patients that completed the 2-year follow-up (20% loss to follow-up). Significant improvement in KOOS and IKDC patient-reported outcomes were achieved throughout the study with confirmed hyaline-like cartilage in 22 of 40 patients post-operative biopsies.

Similar complications have been reported in one-stage procedures compared to those observed in ACI and microfractures[25]. Arthralgia, joint effusion, and reoperation were the most common among them[22,25].

Future investigations should evaluate the differences in outcomes when higher cellularity is seeded in the chondral defect or differences in the chondrogenic potential of chondrocytes harvested from different local donor sites.

CONCLUSION

One-stage cartilage restoration using a combination of chondrocytes and BM-MSC is a safe and reproducible surgical procedure with satisfactory short- and mid-term clinical outcomes. Similar or better new synthesized cartilage should be expected in the defect compared to ACI with superior cost-effectiveness. Further research may consolidate one-stage cell-based cartilage restoration procedures as the standard of treatment for focal cartilage injuries.

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ORTHOBIOLOGICS

TARGET OSTEOARTHRITIS

– Written by Angelo Boffa, Stefano Zaffagnini, and Giuseppe Filardo, Italy

INTRODUCTION

Osteoarthritis (OA) is a common disease characterized by progressive deterioration and loss of articular cartilage with concomitant structural and functional changes in the entire joint, involving synovium, meniscus, periarticular ligaments, and subchondral bone. OA affects more than 10% of the world population aged 60 years or older and represents one of the major causes of disability worldwide, with a massive impact on society both in terms of quality of life for the individuals and high costs for the healthcare systems. Clinical features of OA are mostly characterized by signs and symptoms of inflammation, including pain, effusions, and loss of mobility, often associated with significant functional impairment and disability.

Current strategies to manage OA include weight loss, physical treatments, oral medications such as non-steroidal anti-inflammatory drugs and acetaminophen, and intra-articular injection therapies with corticosteroids and hyaluronic acid (HA). These conservative therapies have modest and short-lasting efficacy and are not able to arrest the underlying disease process. Thus, the final treatment is often represented by joint replacement, which is invasive and not free from complications, especially in young and active patients. In this light, research efforts have been made to find new minimally invasive and potentially disease-modifying procedures to address patients with OA in order to delay or avoid surgery. Among these, orthobiologics are gaining increasing interest due to the availability of several promising products with a biologic potential in improving joint tissues healing, ranging from platelet concentrates to minimally manipulated mesenchymal stromal cells (MSCs) obtained from bone marrow or adipose tissue. The evidence for these approaches derives largely from their intra-articular applications to address degenerative joint disease, in particular for knee OA.

This article will describe rationale and clinical evidence of the most used orthobiologics for the management of OA.

RATIONALE

The use of orthobiologic injectables is growing in the clinical practice with the aim to reduce symptoms, restore a satisfactory joint function, and possibly prevent OA progression delaying the need for surgery. These approaches exploit the high concentrations of growth factors, cytokines, and bioactive molecules of blood derivatives, as well as the presence of mesenchymal stromal cells (MSCs) in tissue derived concentrates.

- Platelet Rich Plasma (PRP) has gained increasing attention due to the high concentration of bioactive molecules stored in platelet α-granules, which showed to take part in the homeostasis of joint tissues, being involved in both healing process and immunoregulation. These biologically active proteins seem to be able to promote a positive joint environment, favoring the restoration of a homeostatic balance in OA joints. PRP showed different and heterogeneous mechanisms of action, including the increase of chondrocyte proliferation rate, matrix production stimulation, and inflammation modulation. PRP may also significantly enhance synoviocyte HA secretion and switch synovial angiogenesis to a more balanced status, as well as increase the expression of biglycan and decorin in meniscal cells. Pre-clinical evidence further supports the role of PRP in modulating the intra-articular environment by counteracting inflammation in degenerative joint diseases. PRP injections showed disease-modifying effects in experimental animal studies, attenuating the progression of cartilage tissue damage and reducing the inflammatory reaction of the synovial membrane in OA joints[1].

- Bone Marrow Aspirate Concentrate (BMAC) has been proposed as a promising option for the treatment of cartilage lesions and OA, being a combination of biologically active proteins and cells obtained through a mini-invasive and technically easy procedure. The rationale for the use of BMAC relies on the transplantation of the entire bone marrow niche which contains MSCs, hematopoietic precursors, monocytes, and endothelial cells, as well as a great array of soluble factors. All these are involved in several pathways crucial for cell maintenance and function, differentiation, extracellular matrix production, and for the regulation of cell catabolic/anabolic activities. Bone marrow MSCs showed the ability to differentiate toward several lineages (i.e., chondrocytes, osteoblasts) and to produce growth factors, which may positively affect joint homeostasis and eventually contribute to relief pain and to improve joint function[2]. Accordingly, this combination of cells and bioactive proteins makes BMAC a unique product among currently available orthobiologics, with the rationale of potentially altering OA course.
- Adipose-derived products have been recently proposed as promising alternatives for the management of OA, thanks to the advantages provided by adipose tissue over other MSCs sources. In fact, adipose tissue is easily accessible, abundant, and obtainable with a mini-invasive procedure offering a high number of cells and pericytes (MSCs precursors). Adipose tissue contains approximately 500–2500 times more MSCs compared to the same volume of bone marrow[3]. Moreover, while the number of MSCs contained in bone marrow decreases with age, the available in the adipose tissue is quite stable during life, representing an aspect that is very beneficial for an elderly population[4]. Adipose tissue can be processed at the point of care into cell suspensions, producing the Stromal Vascular Fraction (SFV), or as microfragments, producing the Micro Fragmented Adipose Tissue (MF-AT). Compared with bone marrow-derived MSCs, adipose-derived MSCs showed to be more genetically stable, with higher proliferative and differentiation capacity, longer telomere length, and lower senescence ratio[5].

CLINICAL EVIDENCE

Platelet Rich Plasma (PRP)

PRP is gaining a large interest in the clinical practice as a minimally invasive injective OA treatment thanks to its safety, low costs, and simple preparation technique to obtain its biologically active content (Figure 1). Since the first clinical applications, several studies supported the safety and effectiveness of PRP for the treatment of knee OA, demonstrating satisfactory results in terms of reduction of pain-related symptoms and functional improvement up to 12 months. These benefits have been observed especially in young patients and early OA stages. Despite the large placebo effect ascribed to intra-articular injections, in particular when dealing with new products such as PRP, a recent meta-analysis on 34 randomized controlled trials (RCTs) showed that PRP injections provided a statistically and clinically significant improvement in patients with knee OA compared to saline injections at 6 and 12 months of follow-up, without increasing the risk of adverse events[6]. Moreover, PRP injections provided better clinical results than other commonly used injective strategies such as corticosteroids or HA at 6 and 12 months of follow-up[6]. Some studies suggest that the clinical improvement provided by PRP can be perceived by patients also beyond 24 months, with a subsequent gradual reduction over time[7]. A recent retrospective study and survival analysis also showed that PRP may delay the need for total knee arthroplasty (TKA) with a median of 4 years and with a survival rate of 85% at 5 years of follow-up[8].

Recently, some researchers investigated the effectiveness of subchondral injections of PRP to address patients with knee OA. Sànchez et al analyzed the combined

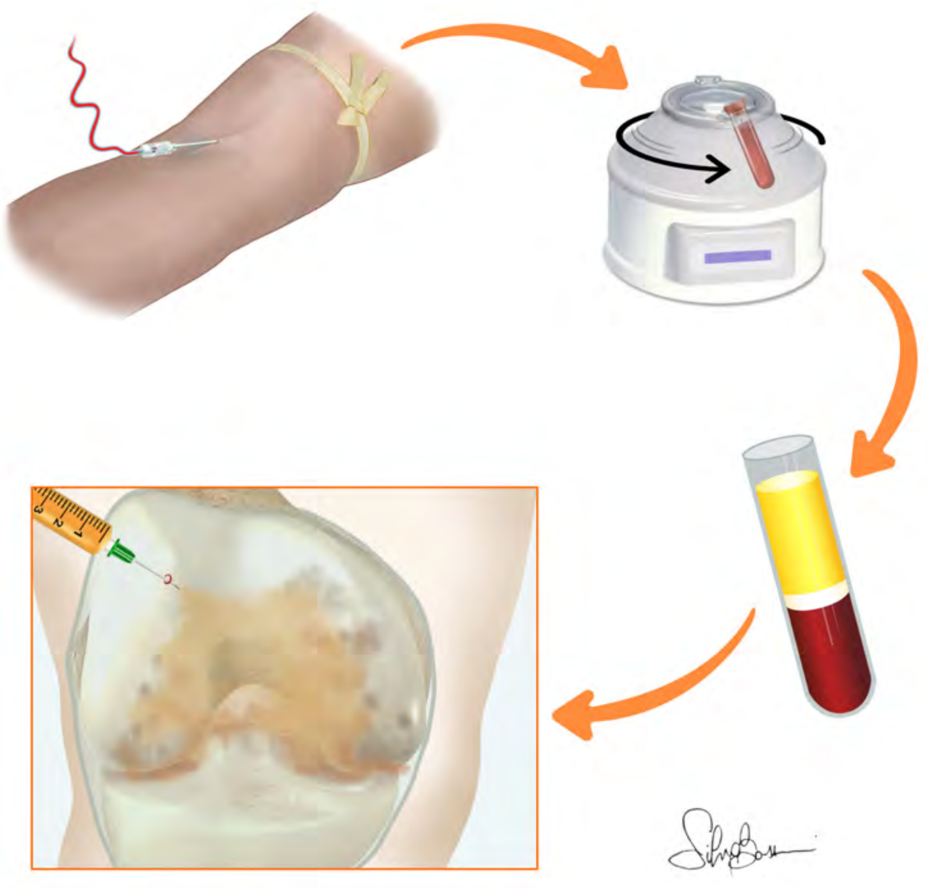

Figure 1: Peripheral venous blood is harvested from the patient arm and then processed using a centrifuge to separate the blood components obtaining three layers: erythrocytes (45% of whole blood), "buffy coat" (<1% of whole blood), and platelet poor plasma (PPP - 55% of whole blood). Erythrocytes and PPP are discharged to obtain the layer concentrated in platelets (with or without leukocytes) - PRP, which is injected into the knee.

use of subchondral and intra-articular PRP injections reporting the safety of this strategy, with rare and mild adverse events, and supporting its effectiveness in improving functional status and reducing pain, with a relatively low rate of conversion to TKA[9]. More recently, the same group observed better clinical results at 6 and 12 months in favor of the combination of subchondral and intra-articular PRP injections compared to intra-articular injections alone in 60 patients with a prevalent grade 3 knee OA according to the Ahlbäck scale, confirming the importance of directly targeting also the subchondral bone area[10]. The biological effects of subchondral PRP injections have been evaluated by Lychagin et al through the measurement of the levels of the serum cartilage oligomeric matrix protein (COMP), an early biomarker for the remodeling of articular cartilage, in OA patients treated with subchondral PRP injections[11]. They found a consistent increase of serum COMP levels after the procedure, which in the authors conclusions could reflect the effects on cartilage turnover resulting from the subchondral treatment.

Despite the promising clinical results, no consensus or guidelines still exist among the scientific societies of orthopedic surgeons, rheumatologists, and physiatrists, on the most suitable indications for the use of PRP in the treatment of OA. This is likely due to the relatively new evidence as well as the lack of a standardized protocol and to the wide availability of different PRP preparation methods. These can yield products with different composition and characteristics in terms of number of platelets and leukocytes, volume of whole blood harvested or PRP obtained, storage procedures, activation method of platelets, formation of a fibrin matrix, etc... Many questions remain open, and all this makes it very difficult to merge and analyze clinical results of different studies and to gain a full understanding of the real benefits of this biological approach. Further studies will have to investigate all these aspects to better understand the potential and limitations of PRP for the treatment of joints affected by OA.

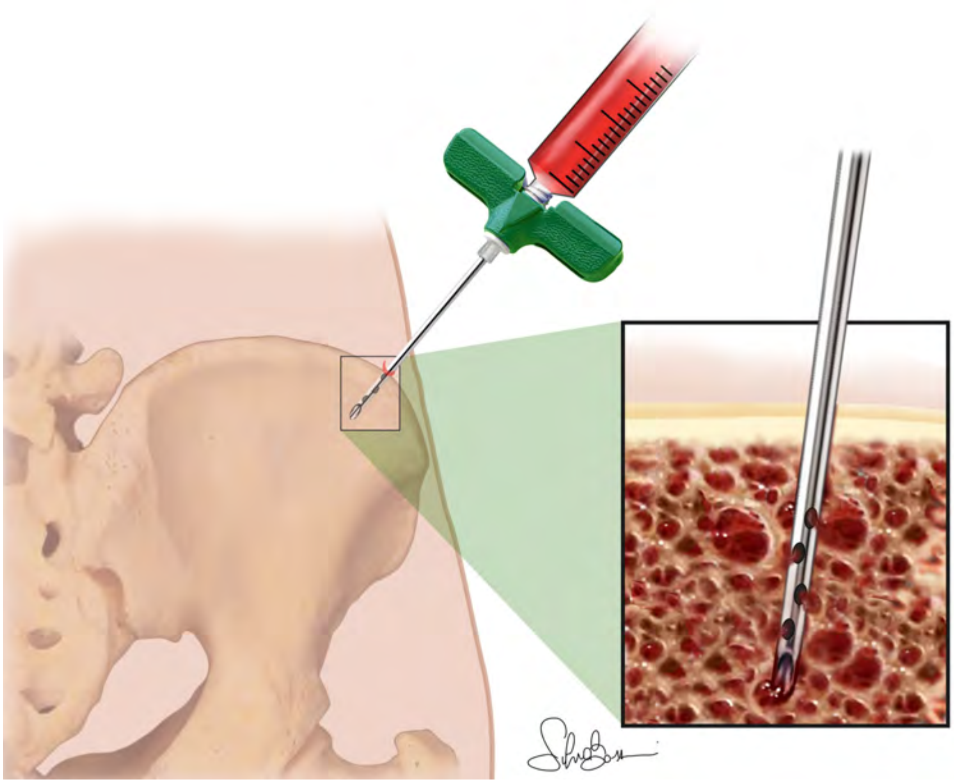

Figure 2: In a one-step technique the bone marrow is harvested from the iliac crest. The procedure is performed under spinal loco-regional anesthesia. The trocar is inserted and advanced, and bone marrow is harvested with a syringe coated with anticoagulants. The bone marrow aspirate is centrifuged to obtain the bone marrow aspirate concentrate (BMAC).

Bone Marrow Aspirate Concentrate (BMAC)

BMAC has been widely applied in the clinical practice for the treatment of cartilage lesions first and, more recently, it has been proposed as a promising mini-invasive approach to treat degenerative orthopedic conditions like knee OA (Figure 2). Only a few pre-clinical studies analyzed the effects of BMAC injections to address OA joints. In vivo OA models reported that BMAC provided better results in terms of macroscopic, histological, radiological, and immunohistochemical findings compared with control groups (saline, HA, or PRP)[12]. The available clinical studies investigating the use of BMAC to address OA evaluated mainly the knee injective treatment, while only few studies focused on shoulder, hip, or ankle OA[12]. Despite an overall poor methodology and a significant heterogeneity, these preliminary trials reported promising results for OA in terms of safety and effectiveness for symptoms management of this intra-articular approach, which led to pain relief and knee function improvement. Nevertheless, the few comparative studies available in the literature did not show BMAC superiority over the other intra-articular options, and the only placebo-blinded RCT was not able to prove BMAC superiority over saline at 12 months of follow-up[13].

A new application of BMAC has been recently suggested to further exploit its potential by targeting the subchondral bone, which is commonly involved in the OA processes. The subchondral BMAC administration demonstrated promising clinical results in preliminary reports on knee OA. The first evidence has been reported in an RCT by Hernigou et al, which evaluated 30 young patients with bilateral knee OA secondary to osteonecrosis and treated with subchondral BMAC injections on one side, and with TKA on the other side. BMAC injections provided similar clinical outcomes compared with TKA, but a lower complication rate and a quicker recovery[14]. The same authors analyzed 140 patients with medial knee OA planned to undergo bilateral TKA and treated with subchondral BMAC injections on one side and with TKA on the other side. Subchondral BMAC injections provided an effect on pain that allowed to postpone or avoid TKA up to 15 years of follow-up, with only 25 patients requesting TKA in the knee treated with BMAC[15]. Hernigou et al also described the superiority of subchondral BMAC injections

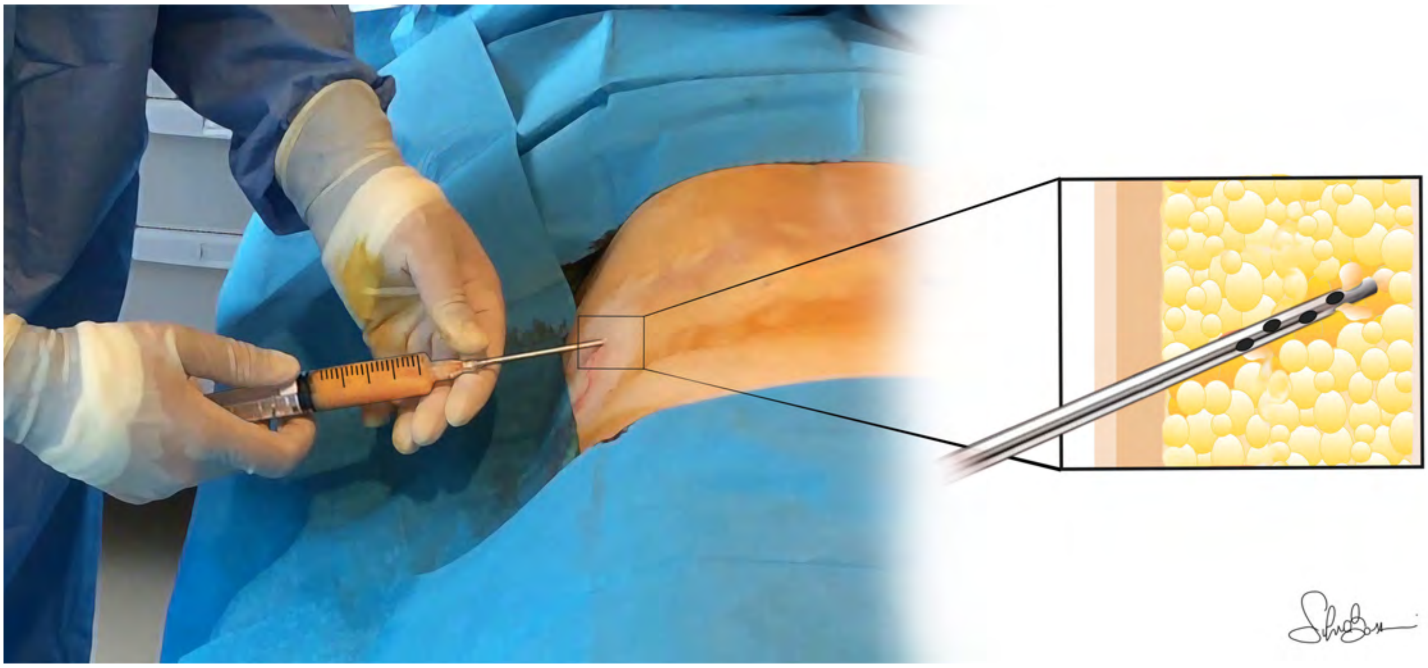

Figure 3: Adipose tissue is harvested from the subcutaneous abdominal fat (usually the lower or lateral abdomen). The site is injected with adrenaline and lidocaine and then the adipose tissue is collected with a blunt cannula. The harvested fat is immediately processed (mechanically or with enzymatic digestion, with or without centrifugation according to the specific procedure) for SVF or MF-AT one-step injection.

over intra-articular BMAC injections in an RCT on 60 patients with bilateral knee OA, showing in the subchondral group a lower yearly arthroplasty incidence (1.3% versus 4.6%) and higher clinical and magnetic resonance imaging (MRI) improvements at 2 years of follow-up[16]. A recent prospective multi-centric study of Kon et al evaluated the combined approach of subchondral and intra-articular BMAC injections to address 30 patients with symptomatic knee OA with associated subchondral bone alterations. The authors documented a significant clinical improvement up to 12 months of follow-up, while the MRI evaluation showed a reduction of bone marrow edema, suggesting that targeting with BMAC both subchondral bone and joint environment can provide promising results to treat knee OA[17].

Still, the application of BMAC to address patients with OA joints has a limited scientific support and more high-level studies are needed to understand if this product could represent a valid option among the different biological treatment strategies. Moreover, many aspects remain to be clarified to optimize the potential of BMAC, including methods of harvest and centrifugation, timing of injection, and application modality, and to provide a standardized method targeted to the OA treatment.

Adipose-derived products

Adipose tissue can be obtained with a minimally invasive procedure and processed at the point of care into cell suspensions, producing SVF or MF-AT (Figure 3). SVF is generally obtained with an enzymatic method, which consists of digesting the lipoaspirate with collagenase to break down the matrix and release MSCs and other cells. Subsequently, the collagenase is removed by dilution and washing, followed by centrifugation[18]. SVF application showed safety, feasibility, and effectiveness for the treatment of joints affected by degenerative cartilage lesions and OA in pre-clinical studies, improving of the quality of the cartilage with respect to control groups[18]. Several trials analyzed SVF injections in the clinical practice, reporting a low rate of adverse events and improvement in pain and functional outcome scores in patients with knee OA, although most studies are case series without a comparative arm[19]. A recent double-blind placebo-controlled RCT on 39 patients with knee OA showed a statistically significant improvement in the SVF group compared to the control group up to 12 months of follow-up, although MRI did not reveal changes in cartilage thickness after treatment[20]. Moreover, intra-articular SVF demonstrated better clinical and imaging findings at 12 months compared to HA in an RCT on 32 patients with knee OA[21]. Despite these promising findings, these studies analyzed only small sample sizes and thus further high-level studies are needed to clarify the real therapeutic potential of SVF.

MF-AT treatment is also gaining interest in clinical practice, since it is obtained through a simple, minimal mechanical manipulation that leads to a progressive reduction in the size of adipose tissue clusters with the elimination of oil and blood residue. MF-AT approach has the advantage of preserving cell integrity and tissue microarchitecture, providing a high number of cells and growth factors, without the need for enzymatic or expansion treatment[22]. The benefits of this products were observed in in vitro studies, reporting a better (qualitatively and quantitatively) secretion of growth factors and cytokines involved in tissue repair compared to the enzymatic methods[23]. Moreover, MF-AT contains a significantly higher concentration of exosomes secreted by MSCs compared to the enzymatic method, suggesting a better preservation of the paracrine potential of adipose MSCs and

> **The management of OA remains an important challenge for physicians, and orthobiologic approaches can play a key role thanks to their potential in modulating the articular environment.**

thus their efficacy[24]. To this regard, a recent in vivo pre-clinical study reported better results in terms of protection of the articular surface from the joint degenerative OA processes in rabbits treated with MF-AT compared to those treated with SVF or expanded adipose-derived MSCs[25]. MF-AT injections showed promising results also in the clinical practice in patients with knee OA, with a low number of adverse events and a significant improvement in pain, function, and quality of life[26,27]. Despite the growing number of clinical studies focusing on intra-articular MFAT injections for knee OA, high-level studies comparing the effectiveness of this product with other injectables are still limited. Therefore, further studies are needed to clarify the potential of MF-AT and the advantages versus other injective options to treat OA joints.

CONCLUSIONS

The management of OA remains an important challenge for physicians, and orthobiologic approaches can play a key role thanks to their potential in modulating the articular environment. Several products ranging from PRP to minimally manipulated MSCs strategies are frequently performed in patients with symptomatic OA, although their indications and guidelines are not always clear. Despite the increasing use in the clinical practice, evidence on these injective approaches is still limited and not able to guide clinicians in choosing the best product, indication, formulation, injections schedule, as well as many other aspects related to both products and patient management. Further research efforts are needed to define potential and limitations of each biological strategy for the conservative treatment of joints affected by OA.

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Available at www.aspetar.com/journal

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SONJA VASIC

– Interview by Lana Krzman

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The best Serbian women's basketball player Sonja Vasic, who is also a newly crowned Women's EuroBasket champion of 2021, is a flag bearer of her country in the opening ceremony of the Tokyo Olympic Games. After 17 years of successful professional basketball in the USA and Europe, multiple medals, champions league and national titles, she decided to finish her outstanding sports career after the Tokyo 2020 Olympic Games.

How did she get to the top? A combination of dedication, hard work, pain, and tremendous family support.

Here the 32-year-old athlete shares with our colleague Dr Lana Krzman her love for basketball, experience from her long career, and advice for children who are just starting to play sports.

You have announced that after the Olympic Games in Tokyo you will end your playing career. How difficult was it for you to be an elite athlete?
Very complex question that would be difficult to answer in one sentence. A professional sports career evolves through phases and at the beginning the athlete can't be aware of the temptations and adversities that he/she must face. We, professional athletes, have to change our priorities with time, but the difficulties stay the same: injuries, absence from home, separation from family and friends, not being there to support them when in need... Life of elite athletes seems to be extravagant and interesting, but the truth is far from that. I was one of the lucky ones, thanks to basketball, that lived some extraordinary moments, travelled the world, made lifelong friendships, learned a different language, played some good games, and won many trophies.

You have played in USA and several European countries: Serbia, Russia, France, Spain. What are the main differences in their approach to women basketball?
USA has the best organised women basketball in the world. They have a well-developed system and high ethical standards; all players are respected and there is always someone who is taking care of an individual athlete and her needs. The situation with European clubs is much different. Financially, we can sometimes reach better contracts, but this is not a result of a developed system, and it is common to depend on someone's good will. European women

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SONJA VASIC

CAREER HIGHLIGHTS

SERBIA WOMEN'S NATIONAL TEAM

FIBA WOMEN'S EUROBASKET:

2021 Gold medal

2019 Bronze medal

2015 Gold medal

OLYMPIC GAMES:

2016 Bronze medal, Olympic Games Rio 2016

MEDITERRANEAN GAMES:

2009 Silver medal, Italy

CLUBS

EUROLEAGUE CHAMPION:

2014-15 USK Praha

2009-10 Spartak Moscow Region

2008-09 Spartak Moscow Region

FIBA EUROPE SUPERCUP WOMEN WINNER:

2015 USK Praha

2009 Spartak Moscow Region

INDIVIDUAL ACHIEVEMENTS

2021 EuroBasket Most Valuable Player

3x EuroBasket All-Tournament Team: 2015, 2019, 2021

2x Serbian Player of the Year: 2016, 2019

2007 Europe Young Player of the Year Award

2016-18 Played for Phoenix Mercury in WNBA

2012 Played for Chicago Sky in WNBA

basketball clubs are usually owned and managed by individuals and often serve as toys for them.

How does the medical treatment differ between countries where you played?

Again, USA has the best organised health cover of injured players. The medical care we were receiving was always of the highest standards, professional and with guaranteed competence. In Europe, although the officials were willing to invest in the players' contracts, they never reached adequate medical care. It is strange that a player's health seemed like a luxury. In the end, even with great financial motivation, a player who is often off the court due to injuries cannot really contribute to the team. Last year, with a lot of pressure from the players, the medical care started to change for the better, but unfortunately the medical care is still far from optimal.

What are, in your opinion, the most important qualities of a team doctor?

A good team doctor must be competent, to know and understand athletes, and to always be present, not only during the games but during the training as well.

Throughout your basketball career you had numerous injuries, two times your left knee was operated for ACL rupture.

That is true. Basketball is a contact sport with well-known high rates of injurie. By the way I play the game, I exposed myself to an

Image left: Sonja Vasic with the MVP best player trophy at the Women's EuroBasket 2021. Spain, June 2021.

Image below: Vasic playing for ZVVZ USK Prague at the FIBA EuroLeague Women. Russia, April 2017.

even higher risk of injuries. For that reason, some people advised me to change the way I play the game. I chose not to accept their advice because I didn't want to lose my "player's identity".

After my second operation/revision/ of ACL most of my friends believed that was the end of my professional basketball career. The chances to return to play on the pre-injury level were only about 30%.

That reality motivated me to work even harder. Today I believe that this experience made me a much stronger person mentally.

Was that early experience a reason to hire and consult other experts in the discipline of sports medicine/sports science?

Sure, I concluded that if I wanted to continue to pursue a professional basketball career, I had to reinforce my medical team with other experts. I engaged with a personal fitness coach, I started to consult on a regular basis with a sports psychologist and a sports nutritionist. They all helped me significantly to return to the same level as I was before my injuries.

I have the impression that they helped me to prolong my career until today.

It is interesting to mention one small detail from working with a sport psychologist. He has helped me to understand that basketball is a dynamic sport and small mistakes are part of the game. Before, as a perfectionist by nature, I would spend hours on the additional training to punish myself for making mistakes.

What is your experience with sports injuries prevention program, especially prevention of knee injuries?

After revision surgery of ACL, preventive exercise become part of my daily activities. Each day for a half an hour before training I would do different exercises to strengthen the active stabilisers of the knee. Many times, doctors openly advised me to end my professional basketball career because of my left knee. I am sure that these 30 minutes of daily exercise extended my sport's career to the present day.

You have had contact with many doctors; what is your impression, how well did they understand the requirements and mentality of the top athletes?

In my experience they are all very different. Some of them understand that tolerance for effort and pain is very high because we are a category of people that is highly motivated to go back to competing. The majority have difficulty to understand our extreme limits and frequently they see us as the general, not sports population. Fanaticism in training and effort is always present among top athletes when they are working towards the "ultimate goals".

Image right: Sonja Vasic playing for Uni Girona in the Catalan Basketball League. Spain, September 2020.

Image below: Vasic during the WNBA match between the Phoenix Mercury and the Washington Mystics. USA, June 2016.

There is often no logic in our behaviour, so for an inexperienced doctor it's very difficult to fully understand some of the things we do.

What advice would you give to young girls who started to play sports, especially to those who dream of becoming a champion?

I always advise young kids, girls, and boys, to play sports because sport is good for their health and development. By participating in sports, you will strengthen your personality, you will be open to new views and become more mature, independent person, which is very important to young female population.

For top female athletes, a successful career gives an opportunity to be able to protect, encourage and advise the female population.

For young females who dream of becoming the next champions, they have to understand that the road is long and rocky, and percentage of full success is extremely low in practice. In sport, it is very important to know when to stop with your project.

It is not just about top athletes to choose the right moment to end their professional careers. It is also about children and their parents to know when to stop with a dream about a professional sport's career. These are not easy decisions to make.

Image: Serbia´s National Team players celebrate after winning the Women's Eurobasket final match against France on June 27, 2021 in Valencia, Spain.

Do you think that enough attention is given to mental health of young female athletes?

For a long time, it was a taboo topic in sports, skilfully concealed from the public's eyes. Fortunately, in recent years this has been talked about and it has been accepted that only in stable, transparent, and harmonious environment a sport success can occur. Mutual respect between players and coach is essential.

At the beginning of my career, the coaches where very nervous, angry, and always very loud. Players had no say. It was considered at that time that this type of behaviour was necessary to motivate the female team. When I signed to play for one French club I was surprised by my new coach's approach. He was always cool, never raised his voice, he was modest, but he was equally a very successful coach. In that moment, I realised the importance of sports psychology in a coach's education and I am glad that today it lived in practice.

Is it an advantage in women basketball if you have a female coach?

In my opinion it doesn't matter if the coach is male or female, it is much more important that he or she is professional, honourable, and sports educated person. We are lucky in Serbia to have Marina Maljkovic as the national team coach. She understands us very well and have all qualities of a top coach. She created a fantastic atmosphere in the National Team and the end results are many medals in international competition. So, I am very grateful to my coach. Maybe as a woman it helped her to understand better our mental states.

Now as you are approaching the end of your very successful basketball career, to whom are you the most grateful for it?

First, I am grateful to my family, especially to my father who was involved in sport all his life, for being by my side when it was necessary for me to make the most important decisions. I am also grateful to my mother and my sister who have dedicated a large part of their lives to me and my basketball dream. I knew through all these years that I had the full support of my family, which was very important for me. This "team" was later joined by my husband Milos, who is also an Olympian.

Both of us represented Serbia at the Olympic Games in Rio – he in rowing and I in basketball. In a few days we are once again going to participate in Tokyo, seeing that finally both of us are Covid-19 negative.

Good luck in Tokyo and thank you very much for you time!

Lana Krzman M.D.

Image: Flag bearers Sonja Vasic and Filip Filipovic of Team Serbia during the Opening Ceremony of the Tokyo 2020 Olympic Games. July 23, 2021 in Tokyo, Japan.

ASPETAR UPDATES

RESEARCH UPDATES
SURGICAL UPDATES
INDUSTRY NEWS

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ASPETAR RESEARCH

UPDATES

– Moderated by Marco Cardinale Ph.D.
Qatar

Commonly used clinical criteria following ACL reconstruction

The aim of this study was to assess objective measures of gait and functional tests to examine their associations in athletes who had recently commenced running after ACL reconstruction. 65 male athletes with a history of ACL reconstruction were included in the stud and the main outcome measures were: time from surgery, isokinetic knee extension/flexion strength (60°/s), and peak vertical ground reaction force (pVGRF) measured during running using an instrumented treadmill. We also investigated if a range of recommended isokinetic thresholds (e.g. > 70% quadriceps limb symmetry index) affected the magnitude of pVGRF asymmetry during running.

There were significant relationships between quadriceps (r = 0.50) and hamstrings (r = 0.46) peak torque and pVGRF. Quadriceps peak torque explained a quarter of the variance in pVGRF (R2 = 0.24; $p < 0.001$). There was no association between running pVGRF and time from surgery. The study concluded that current clinical criteria including time from surgery and isokinetic strength limb symmetry thresholds were not associated with lower pVGRF asymmetry measured during running. Quadriceps strength is important, but 'minimum symmetry thresholds' should be used with caution.

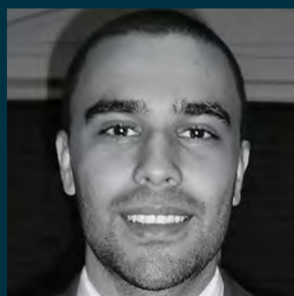
Read PJ, Auliffe SM, Thomson A. Commonly used clinical criteria following ACL reconstruction including time from surgery and isokinetic limb symmetry thresholds are not associated with between-limb loading deficits during running. Phys Ther Sport. 2021 May;49:236-242. doi: 10.1016/j.ptsp.2021.03.010. Epub 2021 Mar 23. PMID: 33812124.

Paul was a Clinical Research Scientist, specialising in the assessment of ACL injuries in Aspetar. During his time in Qatar, he was instrumental in developing and managing Aspetar's Clinical Assessment Unit. Currently, Paul works at Institute of Sports Exercise & Health as a General Manager for HCA UK.

Association Between Injury Mechanisms and Magnetic Resonance Imaging Findings in Rectus Femoris Injuries

The objective of this study was to describe the injury mechanism and its association with magnetic resonance imaging (MRI) injury findings in acute rectus femoris injuries.

Male professional football players older than 18 years playing in a national football league, referred for injury assessment within 7 days after an acute rectus femoris injury, with a positive finding on MRI.



There were 105 injuries in total, with 60 (57.1%) and 45 (42.8%) injuries from the retrospective and prospective cohorts, respectively. Kicking was the injury mechanism in 57 (54.3%) of all acute rectus femoris injuries, sprinting represented 32 (30.4%), and 16 (15.2%) were classified as others. There were 20 (19.05%) free tendon, 67 (63.8%) myotendinous junction and/or intramuscular tendon, and 18 (17.1%) peripheral myofascial located injuries. All free tendon injuries were related to kicking and graded as a complete tear of at least one of the tendons in 15/20 (75.0%) cases.

Kicking seems to be an important mechanism related to complete ruptures and injuries occurring at the proximal free tendon. Sprinting was the other most common mechanism but was never associated with injury to the proximal free tendon.

Geiss Santos RC, Van Hellemnondt F, Yamashiro E, Holtzhausen L, Serner A, Farooq A, Whiteley R, Tol JL. Association Between Injury Mechanisms and Magnetic Resonance Imaging Findings in Rectus Femoris Injuries in 105 Professional Football Players. Clin J Sport Med. 2021 May 26. doi: 10.1097/JSM.0000000000000935. Epub ahead of print. PMID: 34050059.

Dr Rafael Geiss Santos is a sports medicine physician in Aspire Academy. Before joining Aspire he was the team physician of the Brazilian Basketball teams and a Sports Physician in the Brazilian FIFA centre of excellence.

Lower medial hamstring activity after ACL reconstruction during running: a cross-sectional study

Anterior cruciate ligament reconstruction (ACLR) predisposes footballers for subsequent ACL and hamstring (HS) injury. This case series examined HS muscle activation patterns during the running in ACLR patients (bone-patellar tendon-bone (BTB) and (HS) graft) after completion of functional criteria allowing return to training.

Electromyography (EMG) recorded from medial and lateral HS bilaterally during treadmill running (12, 14 and 16 km/hour) from 21 male ACLR patients on average 7 months from surgery (5-9) that underwent (HS) (n=12) or BTB reconstruction (n=9) were compared with 19 healthy runners. Main outcome measures: EMG signal was normalised to peak during the running. Pairwise comparisons were made for each muscle group examining stance and swing activation for mean and peak EMG for each patient group and leg.

Significantly lower relative peak activation in stance (not swing) phase for medial HS was seen for all conditions with effect sizes ranging from -0.63 (controls, BTB non-injured leg) to -1.09 (HS injured). For lateral HS only BTB injured were significantly lower in stance phase (-1.05).

ACLR patients show neuromuscular alterations during different phases of running. The finding of reduced medial HS activity in stance phase might have implications for knee instability and HS muscle injury on resumption of sport.

Einarsson E, Thomson A, Sas B, Hansen C, Gislason M, Whiteley R. Lower medial hamstring activity after ACL reconstruction during running: a cross-sectional study. BMJ Open Sport Exerc Med. 2021 Mar 11;7(1):e000875. doi: 10.1136/bmjsem-2020-000875. PMID: 33782638; PMCID: PMC7957131.

Einar Einarsson is a Senior Physiotherapist in Aspetar specialised in muscle and joint injuries and return to play.

Isolated meniscus injuries in skeletally immature children and adolescents: state of the art

This narrative review was published with the aim of updating current knowledge on meniscus injuries in children and adolescents.The prevalence of isolated meniscal injuries in children and adolescents is low; however, we see an increase mainly due to intensified sports-related activities at an early age. A meniscal repair should be attempted whenever possible as children present with increased meniscal healing potential. The diagnosis and management of meniscal tears involve both patient factors and tear characteristics: size, anatomical location and associated injuries. Special attention should be given to the feature of discoid menisci and related tears as they require a specific management plan. Based on current evidence, surgical tips were provided.

The all-inside meniscal repair can be very difficult to perform in children and adolescents because of their smaller knee size and may be necessary to modify it to an inside-out technique using a posterolateral incision and a cannula system to protect the peroneal nerve, popliteal vessels and the tibial nerve (preventing deep posterior perforation).

For meniscal root tear fixation in the paediatric population with open physis, it can be useful to use retrodrilling or anchor devices to avoid further damage of the physis.

Saucerisation technique should be performed cautiously to a normal rim (6–8 mm) and to avoid removing too much meniscal tissue. The stability of the peripheral rim of the meniscus should be probed and, if unstable, should be treated with meniscal repair to the capsule.

Vinagre G, Cruz F, Alkhelaifi K, D'Hooghe P. Isolated meniscus injuries in skeletally immature children and adolescents: state of the art. J ISAKOS. 2021 May 21:jisakos-2020-000496. doi: 10.1136/jisakos-2020-000496. Epub ahead of print. PMID: 34021035.

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Endoscopic Carpal Tunnel Release

Advantages for athletes

– Written by Jonny K Andersson, Qatar, and Elisabet Hagert, Sweden

Endoscopic carpal tunnel release (ECTR) techniques were developed as an attempt to avoid problems occasionally experienced following Open carpal tunnel release (OCTR), namely scar tenderness and pillar pain. The advantage of ECTR is the small scar, not localized in the vola, the good visibility at the TV monitor with no need for loops, and compared with OCTR - it is less time consuming, if the surgeon and the staff are used to the procedure. The learning curve for performing ECTR is although longer than for OCTR, and the procedure should be performed by a Hand Surgeon used to arthroscopic/endoscopic techniques.

Operative technique

Popular approaches include the dual-portal technique of Chow and the single-portal technique of Agee[1,2].

Using the Chow technique, proximal and distal incisions are made deep to the transverse carpal ligament (TCL). The endoscope and blade assembly are passed from the proximal incision through the distal incision, deep to the TCL. The distal TCL is released using a probe knife. A second cut is made in the midsection of the TCL with a triangular knife and joined to the first cut using a retrograde knife. The endoscope is then repositioned and in a similar fashion the probe knife used to cut the proximal TCL. A retrograde knife is inserted into the midsection of the TCL and drawn proximally to complete the release.

In the Agee ECTR, a small transverse skin incision is made at the ulnar border of the palmaris longus tendon, midway between the flexor carpi ulnaris and radialis, and proximal to the wrist flexion creases. A distally based forearm fascia flap is elevated to reveal the proximal edge of the TCL. With the wrist in extension, the endoscopic blade assembly is inserted into the canal in line with the ring finger. The TCL is visualized and divided distally to proximally.

Endoscopic carpal tunnel release versus Open carpal tunnel release

Both OCTR and ECTR are practiced widely, with proponents of both techniques continuing to debate the merits of one over the other. A common argument in favor of ECTR over OCTR has been reduced postoperative pain and a shorter return to vocational activities. Although these findings have been borne out in some studies, three to five other studies show that any differences between techniques in patient symptoms, function, and satisfaction equalize by 1 year[6,7]. Supporters of OCTR have, in turn, cited a higher incidence of postoperative neurovascular complications as a reason to avoid ECTR[8]. More recent studies have failed to support this higher risk in ECTR[3,4,6,7,9]. Cost has been another factor in the debate between OCTR and ECTR. A 1998 cost-effectiveness analysis comparing the two techniques concluded that ECTR is cost-effective provided major complications occur 1% less often than in OCTR[10]. In a recent publication on the cost-effectiveness of ECTR, it was found that ECTR is beneficial from a societal standpoint, in that it leads to faster return to work and higher quality-adjusted life years (QALY).

A transverse 1 cm long incision at the ulnar side of wrist, leading to an almost invisible scar and low incidence of pillar pain, as well as leading to equal, perhaps greater, functional outcome for the patients, is in our opinion reasons enough to recommend ECTR as compared with an open procedure. It is, of course, of essence that the surgeon has good experience and command of the endoscopic technique.

Endoscopic carpal tunnel release – Contraindications and relative contraindications

- Synovitis along the flexor tendons (relative contraindication).
- Reoperation of carpal tunnel syndrome (CTS).
- Concomitant distal radius fractures, carpal fractures and dislocations as well as other injuries, where open surgery is indicated.
- Malunion of distal radius fractures with abnormal alignment.
- CTS due to infection.
- Tumors in the carpal tunnel or thenar/hypothenar, e g lipoma, ganglia.
- Surgeon not used to the technique.

Sometimes, but seldom there are risks for impaired visibility during the endoscopic procedure and synovitis not expected can be found intraoperatively.

Figures 1 to 3:
Endoscopic Carpal Tunnel Release surgical procedure step-by-step.

TAKE HOME MESSAGE

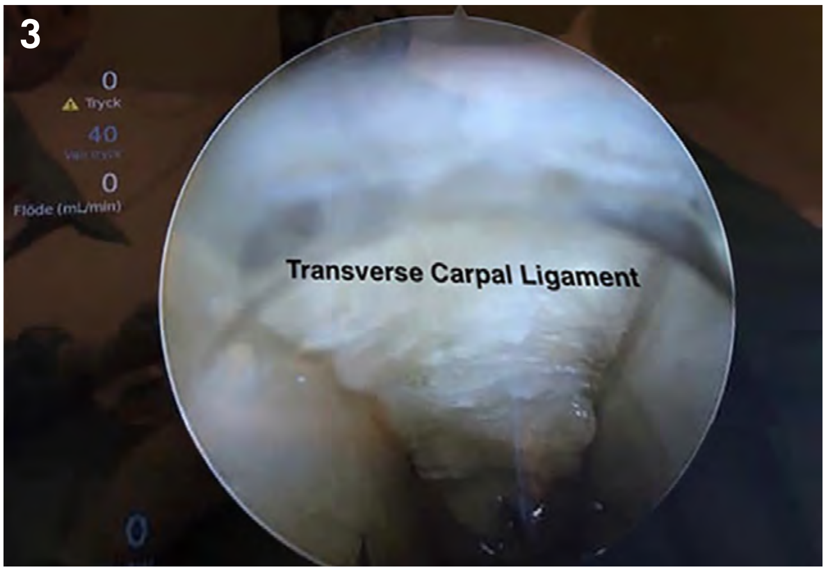
The advantage of ECTR is the small scar, not localized in the vola, the good visibility at the TV monitor.

The procedure should be performed by a Hand Surgeon used to arthroscopic/endoscopic techniques

Patients should always be informed preoperatively when the surgery is scheduled, during the informed consent process and also before the surgical procedure, that the endoscopic procedure may, if necessary, have to be converted to open surgery.

The technique is indicated for a majority of patients and many of them attending Aspetar Hospital with Carpal tunnel syndrome the last year have asked about ECTR, as they heard about the endoscopic technique, being performed abroad.

Endoscopic Carpal Tunnel Release – a wanted, convenient and rewarding method treating carpal tunnel syndrome - can now be provided to the population of Qatar, at Aspetar Hospital.



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INDUSTRY NEWS

– Written by Nathan Riding PhD, Qatar


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Could a hot bath be the secret to Tokyo success?

Environmental physiology

The Tokyo Olympics is upon us, and although a year delayed, the same environmental concerns for athletes persist. The games organisers recently highlighting that "the rainy season is over in Tokyo, and the hot summer has come". Facing the warmest Olympics in decades, although the marathon has been moved 800 kilometres north to the city of Sapporo, the majority of the action will continue in Tokyo as planned. How the athlete prepares for such conditions is thus imperative to health and performance. Heat acclimation has been a mainstay of elite athletes preparations and have been shown to improve endurance capacity and reduce susceptibility to exertional heat illness. It is though seen by some as costly, impractical, and having the potential to disrupt quality training. With this in mind researchers from the University of Bangor recently investigated, among 27 recreational male athletes, whether a simple post exercise hot bath could elicit similar favourable adaptations and provide a cost effective alternative. They ultimately found that by taking a 25-40 minute bath at 40 degrees following treadmill running in temperate conditions for 6 days, it led to larger thermal adaptations in an experimental heat stress exercise test, including earlier sweating and a lower rectal temperature at the end of the trial. By highlighting that there were only modest benefits to exercising in the heat, and this overshadowed by the results of hot water immersion, it could aid in the athletes preparations for competing in the heat.

What to look for when making a return to sport decision following an acute lateral ankle sprain

Sports Medicine

Among both recreational and elite athletes, lateral ankle sprains remain one of the most common musculoskeletal injuries. Given the high proportion of athletes that develop chronic ankle instability, long term associated symptoms, and reoccurrence of the injury, the clinical assessment and return to play management is crucial. In spite of this, there have previously been no guidance for the responsible practitioner on informing the return to play decision. Recently however an international team of experts, including a survey of 155 health professionals from around the globe has led to the formation of such guidance. Based on a 70% or greater consensus among panellists, including both quantitative and qualitative assessment of certain assessment criteria, 5 key domains were identified in the document to facilitate the return to play decision, which were pain, ankle impairments, athlete perception, sensorimotor control, and sport performance. Published in the *British Journal of Sports Medicine* and headed by Dr Smith of the University of Queensland, a 16 step checklist was devised to assess whether the athlete can indeed return to play. The items on the list included pain during sport over the last 24 hours, ankle range of motion, muscle strength, endurance and power. How the athlete felt about the injury including perceived ankle confidence/reassurance and stability, and psychological readiness. A sensorimotor component which includes proprioception, dynamic postural control/balance. And finally sport or functional performance, including tasks such as hopping, jumping and agility; sport-specific drills, and the ability to complete a full training session.


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© Marco Verch/flickr.com (cropped)

An extra 330 calories may be sufficient to restore menses in exercising women with menstrual disorders

Female athlete health

25 million, is the combined total calories burned by the cyclists during the recent Tour de France. It means they must fuel accordingly, indeed up to 6,000 calories per day. The fuelling needs while are extreme in this 3 week race, are also important for athletes across the globe, in order to maintain health, performance, and in avoiding injury. Studies from as early as the 1990s, have however shown that acute exercise is not often followed by a compensatory increase in both hunger and resultant intake of calories. For female athletes it also has the potential to disrupt normal reproductive function, yet until now, little had been known on whether an increase in energy intake leads to menstrual recovery in exercising women with menstrual cycle disorders. Publishing their findings in the journal Human Reproduction, a research team from the Pennsylvania State University, led by Professor De Souza, found that a modest increase in daily energy intake of 330±65kcal is sufficient to induce menstrual recovery in exercising women with oligomenorrhoea or amenorrhoea. The women with the extra calories demonstrated a greater increase in energy intake, body weight, percent body fat and total triiodothyronine. Importantly, of the 40 women with added energy intake, 64% exhibited improved menstrual function, compared to just 19% of the 36 without the extra calories.

Following Christian Eriksen's cardiac arrest over 2000 defibrillators to be donated by the English Premier League

Sports Cardiology

© Stuart Franklin/Getty Images

On Saturday 12th June 2021, at 5.43pm, time stood still. Danish football player Christian Eriksen had just suffered a cardiac arrest. Thanks to the rapid response, prompt cardiopulmonary resuscitation (CPR), and defibrillation, Eriksen was conscious upon leaving the field, and survived. With survival decreasing by 10% every minute, such prompt response is vital. In the English football league all clubs have automated external defibrillators (AED) on match days and during training sessions. Within a 2017 study assessing emergency response facilities in English professional football, while 100% of top tier teams provided training on how to use the AEDs, only 30% of lower league teams provided such education. The availability of AED's and training on their use in grassroots football is lower, and the events of Euro 2020 has led the Premier League partnering with the Football Foundation and the FA to provide and fund over 2,000 AED's to facilities around the United Kingdom. Sport minister Nigel Huddleston told Sky news that he urges clubs to take advantage of the defibrillator fund and the FA's training scheme and give confidence to players that their health and welfare is the top priority."

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Rashford sets new record in penalty heartache

Sports Psychology

11 seconds. This was the time English striker Marcus Rashford waited prior to taking his crucial penalty in the Euro 2020 final against Italy. According to football psychologist Professor Geir Jordet, in 45 years of big tournament competition, nobody has ever waited that long. His research has revealed that successful penalty takers typically take a longer 2.5 seconds to slot the ball in the back of the net, compared to those unsuccessful at a much shorter 0.9 seconds. In this regard, history was not on England's side. A 2009 study from Jordet and colleagues, showing that their prior penalty heartache has been partly attributed to having taken quicker penalties more often than any other nation. The quick relief from the high pressure scenario a touted reason, while a longer wait allows for composure, focusing on the task, and gaining control of the situation. The extra 8.5 seconds Rashford took above the average was, according to Jordet, likely due to pressure. A first major final for 55 years, at home, and, like fellow penalty taker Jadon Sancho, having been substituted on in the final minute for this one task. Nevertheless, by selecting young, non-fatigued strikers, with a history of successful penalties was supported by research. Nevertheless, Rashford remains a national hero, and like other notable stars to miss a penalty such as Lionel Messi, Cristiano Ronaldo and Kylian Mbappe, will no doubt be back stronger.

IN NUMBERS

6% Percentage decrease in respiratory function (FEV_1) pre-post the Tour de France.

100,000 Calories burned per rider in the Tour de France.

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