Chapter 2
Emerging Concepts in Treating Cartilage, Osteochondral Defects, and Osteoarthritis of the Knee and Ankle

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Abstract The management and treatment of cartilage lesions, osteochondral defects, and osteoarthritis remain a challenge in orthopedics. Moreover, these entities have different behaviors in different joints, such as the knee and the ankle, which have inherent differences in function, biology, and biomechanics. There has been a huge development on the conservative treatment (new technologies including orthobiologics) as well as on the surgical approach. Some surgical development upraises from technical improvements including advanced arthroscopic techniques but also from increased knowledge arriving from basic science research and tissue

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engineering and regenerative medicine approaches. This work addresses the state of the art concerning basic science comparing the knee and ankle as well as current options for treatment. Furthermore, the most promising research developments promising new options for the future are discussed.

Keywords Surgery · Autologous osteochondral transplantation · Bone marrow stimulation · Congruency · Alignment · Tissue engineering and regenerative medicine

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Highlights

- The treatment of osteochondral defects and osteoarthritis is complex and multifactorial.
- The most commonly used surgical techniques for the treatment of osteochondral defects include microfractures, fixation, autologous or allogeneic osteochondral transplantation or mosaicplasty autologous chondrocyte implantation, and matrix-induced autologous chondrocyte implantation. So far, no method has been able to consistently achieve repair of osteochondral defects similar to the native tissue.
- Tissue engineering and regenerative medicine strategies promise new options for future treatments of cartilage and osteochondral defects.

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Fact Box 1 – Epidemiology of Osteoarthritis and Osteochondral Injuries of the Knee and Ankle

- Osteoarthritis is the most common joint disease with worldwide prevalence over 241 825 million people.
- The overall prevalence of full-thickness focal chondral defects in athletes has been stated as 36%.
- Osteochondral defects of the knee combined with meniscus injuries account for 3.7% of all injuries among elite football players.
- The incidence of OA in the ankle is considerably smaller than in the knee. The prevalence of symptomatic primary OA in the ankle is lower than 1% of the population.
- Moreover, ankle OA does not seem to increase with aging.
- Osteochondral defects of the talus can occur in up to 70% of acute ankle sprains and fractures.

Fact Box 2 – Osteochondral Defects (OCDs) of the Knee

- The treatment of OCDs and OA of the knee is complex and multifactorial.
- Nonoperative options include chondroprotective pharmacotherapy (glucosamines, chondroitin, diacerein, hyaluronic acid, platelet-rich plasma, and cell-based therapy), nonsteroidal anti-inflammatory medication, and physiotherapy.
- The most commonly used surgical techniques for the treatment of knee OCD lesions include microfractures, fixation, autologous (or allogenic) osteochondral transplantation (OATS) or mosaicplasty autologous chondrocyte implantation (ACI), and matrix-induced autologous chondrocyte implantation (MACI).
- So far, no method has been able to consistently achieve repair of OCD by the hyaline cartilage similar to the native.

Fact Box 3 – Osteochondral Defects (OCDs) of the Ankle

- Etiology of ankle OCD can either be traumatic and non-traumatic.
- Always consider association of ankle sprain or chronic ankle instability in the etiology of OCD.
- Fixation of a large fragment should always be attempted.
- Microfracture is still the most popular treatment.
- Similarly to that observed in the knee, no surgical treatment has proven superiority over any other.
- Tissue engineering and regenerative medicine approaches promise new options for the future.

Fact Box 4 – Tissue Engineering and Regenerative Medicine (TERM): Road for the Future

- The basic triad of TERM includes the combination of cells, scaffolds, and bioactive proteins in the healing process of any tissue.
- Orthobiologics might include conservative treatment by injection therapy including growth factors, hydrogels, cell-based therapy, or even combining gene therapy.
- Orthobiologics aim to improve symptomatic cartilage damage and also envision to delay the progressive joint degeneration.
- There has been a massive development on scaffolds assembling including nanostructure and tridimensional bioprinting.
- The road for the future seems to combine the best possible knowledge of all TERM variables aiming to achieve in the laboratory a tissue which can be matured to achieve similar features as the native and custom-made to the defect.

2.1 Introduction

Traumatic and non-traumatic etiology has been implicated in osteochondral injuries, which might or might not develop to general joint degeneration [1]. Degeneration linked to the aging process, trauma-related injuries, and deteriorating or idiopathic disorders might lead to osteochondral lesions [2]. Cartilage damage has been linked to several etiologies including some, which remain poorly understood to date. It is recognized that OA has a higher incidence in aged people [3]. However, the prevalence of articular cartilage injuries has been reported to be higher in athletes when compared to the general population [4–7]. Sports practice has been increasing worldwide. Taking as an example football (soccer), which is the most played sport worldwide, there are more than 300 million people federated and many more

playing without register [8]. Any high-impact contact sport, moreover at high competitive level, might result in damage of the knee and/or structures, including articular cartilage injuries [4, 5, 9]. The large variability of the OA regarding the etiology, histological findings between individuals and groups, and response to therapies demonstrates that there is still a long way for more advanced understanding of this condition [10].

Nevertheless, cartilage injuries are often a consequence of dynamic and repetitive mechanical joint loading [11–14]. Despite the fact that cartilage is a poorly innervated and irrigated tissue when the damage reaches the subchondral bone, complaints will derive [15], including pain, swelling, catching, and locking [5, 16, 17]. Nevertheless, articular cartilage injuries may be present in asymptomatic people or even athletes. There is controversial data concerning the frequency of knee pain referred by footballers [4]. However, patellofemoral conditions are more frequent in women, while in the ankle, the lesion is mostly present at the talus [18].

If a "pure" cartilage lesion is considered, the damage occurs on the chondrocytes and articular cartilage extracellular matrix (ECM), above the subchondral plate. However, in OCDs besides cartilage injury, the subchondral bone is also involved. Many classifications have been proposed either as global OCD assessment or joint-specific scores [1]. The Outerbridge classification modified by the ICRS (International Cartilage Repair Society) is the one that most frequently used. In brief, it enrolls Grade 0, normal cartilage; Grade I, cartilage softening and swelling; Grade II, partial thickness defect not extending the subchondral bone (<1.5 cm diameter); Grade III, fissures up to the subchondral bone level (>1.5 cm diameter); and Grade IV, OCD with exposed subchondral bone. In some cases of non-traumatic etiology, usually in younger ages, in which a segment of cartilage and subchondral bone detaches from the underlying bone, a vascular or genetic etiology has been proposed, and it is referred to as osteochondritis dissecans [19]. If complete detachment of osteochondritis dissecans occurs, this might lead to intra-articular loose bodies, which further contribute to joint degeneration.

One of the major concerns related to OCDs is the secondary progression to OA [19]. However, it could never have been shown in the ankle joint that the natural history of a focal OCD is secondary OA, while most studies in the knee joint suggest it [1]. This might be related to different joint biomechanics. However, an injury to the hyaline cartilage that is related to a previous trauma is considered as a major risk factor for OA [20]. OA can be a restrictive and painful condition, which is most frequently seen in the knees, hips, ankles, and hands although it might affect any joint. Patients suffering from OA characteristically present pain, episodes of swelling, progressive deformity, and limited range of motion.

OCDs or any cartilage damage, if not adequately dealt with, may result to an earlier onset of joint degradation and osteoarthritis (OA) [21–23]. Symptomatic OCDs in any joint may lead to activity-related symptoms and require changes in lifestyle with permanent functional limitations [24–27]. Besides cartilage damage, injuries affecting the subchondral bone are frequent. However, it is still debatable whether these changes precede the biomechanical lesions of the hyaline cartilage or correspond to secondary changes.

Conservative treatments are based on the adaptation of lifestyle, anti-inflammatory or painkiller medications, supplements (e.g., glucosamine, chondroitin), and orthobiologics (hyaluronic acid, growth factors, cell therapies) [10, 28–32]. Surgical treatment ranges from arthroscopy to osteotomies, to partial or total joint replacement or fusion [10, 28, 29, 31]. Clinical history, physical examination, and imaging (standing x-rays, CT, or MRI) are mandatory for diagnosis [19, 31]. For histological assessment in specific cases or research purposes, it is possible to collect tissue and synovial fluid from joint injections of the knee or ankle without major complications [33]. This is particularly useful in rheumatologic conditions.

According to the current reports, OA has been affecting a significant number of people worldwide with a rise over time, and it represents a social and economic burden [34, 35]. Moreover, high-level sports involve high financial impact and intense social media coverage. Considering the athlete as a usually "young person" with a physically demanding profession, important factors such as age, level of completion, time into the season, and career status must be considered [4]. Therefore, dealing with OCDs and OA is a multifactorial social issue.

2.2 Epidemiology

OA is the most common joint disease [36]. It is not easy to define the global prevalence of OA, given the registered variations according to the used definition of OA for assessment, population characteristics (e.g., age, gender), geographic conditions, clinical-based or radiological-based studies, or self-reported OA [36]. One study reports the worldwide prevalence of clinical OA of 241 825 million people [34]. This number is known to be consecutively growing. The number of people with symptomatic OA has increased 71.9% between 1990 and 2013, and it is expected to keep rising in relation to the increase of life expectancy, among other factors [37, 38]. In Europe, the frequency of symptomatic knee OA is ranging between 5.4% and 29.8% [36]. According to the Framingham study and Johnston County Osteoarthritis Project, in the United States, this number was 7% and 17%, respectively [36]. When considering only a population over 45 years old, the OA prevalence ranged from 19% to 28% [36]. Flanigan et al. reported articular cartilage injuries in a cohort of 931 athletes, involving 732 men and 199 women, with a mean age of 33 years old [5]. The overall prevalence of full-thickness focal chondral defects of the knee in athletes was 36% [5]. From these, only 40% were professional athletes. The UEFA Elite Club Injury Study Group (which studies health conditions of 29 elite European football clubs) in the season of 2015/2016 reported that cartilage/meniscus injuries accounted for 3.7% of all injuries [39].

The incidence of OA in the ankle is considerably smaller than in the knee. The prevalence of symptomatic primary OA in the ankle is lower than 1% of the population [40]. Moreover, it does not seem to increase with aging [40].

Osteochondral defects of the talus can occur in up to 70% of acute ankle sprains and fractures [41]. The different incidences and prevalences of OA on both joints most probably are linked to differences in anatomy and biomechanics [10], but no definite conclusions explaining such differences are currently available.

Genetics or geographical influence might be suggested with an observed extreme variation such as the OA is present in only around 1.4% of the urban Filipinos, and increases among some rural Iranian communities up to 19.3% [42]. Moreover, gender might play a role once a high female predominance has been reported [42], suggesting some role of sex hormones in this condition. With such prevalence and the fact that there is no "cure" up to now, treatment will require continuous clinical care, institutional costs, medication, and surgeries, dictating high healthcare-related costs, besides work absence, thus representing a socioeconomic burden [43, 44]. The global impact on diminished economic productivity added to the reimbursement compensation from the impaired and sometimes the need for third-person care further dictates additional costs [43, 45, 46]. According to a recent systematic review, the social costs of OA range from 0.25% to 0.50% of a country's gross domestic product (GDP) [35]. Considering all the aforementioned, this is one of the most relevant healthcare topics and is critical to improve our effectiveness in dealing with these conditions [47].

2.3 Knee Osteochondral Defects

Normal knee hyaline cartilage has optimum biomechanical characteristics adapted to its function and adjustment capacities to the loading stresses exerted at the joint [48]. Nevertheless, when these capacities are exceeded (e.g., by high-impact loading), there is a decrease in the cartilage proteoglycans levels and an increase in the levels of degradative enzymes (e.g., metalloproteases) that ultimately lead to chondrocyte apoptosis [49, 50]. The consequence will be a loss of cartilage volume and biomechanical resistance, peak contact pressures, and ultimately cartilage defects [48]. Moreover, due to its scarce irrigation and innervation, it has very limited healing potential [25, 29, 51, 52]. Due to these biological and biomechanical conditions, cartilage repair remains a challenge in orthopedics, and so far, there is no single reliable method to achieve repair by hyaline cartilage similar to the native [31].

The first approach employed in the treatment OCDs is a conservative treatment [53]. It includes periods of rest, non-weight bearing, prevention of stiffness by an active joint mobilization, neuro-muscle and proprioceptive trainings, as well as use of medication or orthobiologics [31]. Nonoperative options include chondroprotective pharmacotherapy (glucosamines, chondroitin, diacerein, hyaluronic acid, platelet-rich plasma, and cell-based therapy), nonsteroidal anti-inflammatory medication, and physiotherapy [24, 54, 55]. Particularly in the knee joint, conservative treatment often fails, after a variable period of improvement [31, 56]. A substantial number of patients will require surgical management [31].

2.4 State of the Art in the Treatment of Osteochondral Defects of the Knee

The treatment of OCDs and OA of the knee is complex and multifactorial [57]. The goal of treatment is to provide long-lasting relief of complaints and restore function to the maximum possible [4]. The biomechanical features of the knee joint should be considered as complex.

Nowadays, there are several available surgical techniques to approach a focal OCD. The most commonly used surgical techniques for the treatment of these lesions include microfracture (Fig. 2.1), fixation, autologous osteochondral transplantation (OATS) or mosaicplasty autologous chondrocyte implantation (ACI), and matrix-induced (Fig. 2.2) autologous chondrocyte implantation (MACI) [4, 52, 58, 59]. More recently, matrix-induced autologous stem cell implantation (MASI) has been introduced given the higher mitotic rate and other biological features of these cells and constructs [60, 61].

Whenever possible, fixation of a large OCD with underlying bone (Fig. 2.3) should be attempted once it represents the most "conservative" surgical approach

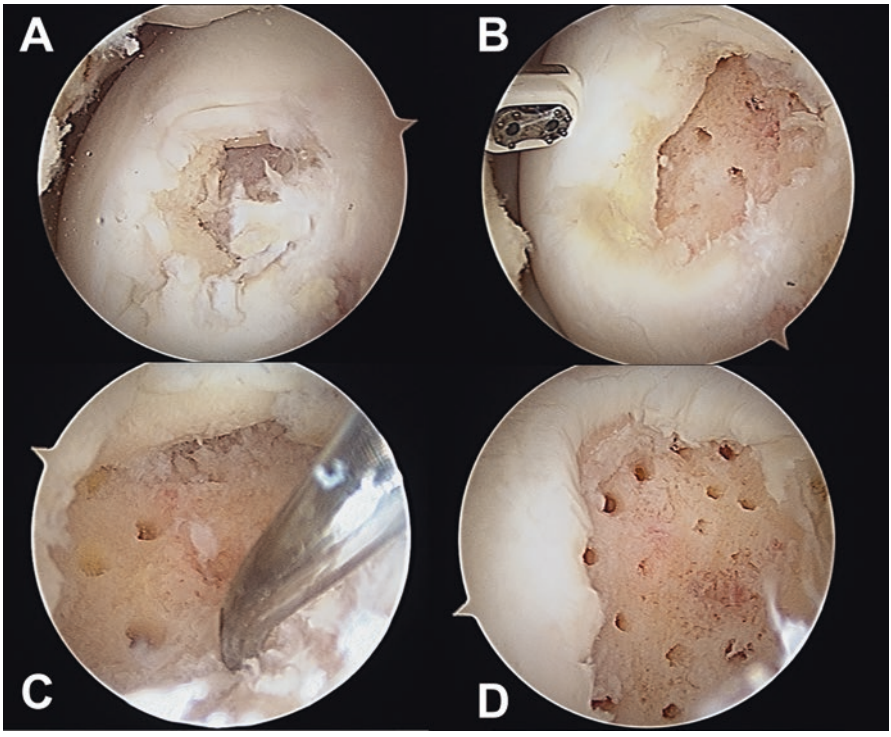

Fig. 2.1 Medial condyle grade IV osteochondral defect (**A**), debridement and microfractures with visible holes on the bone (**B**–**D**)

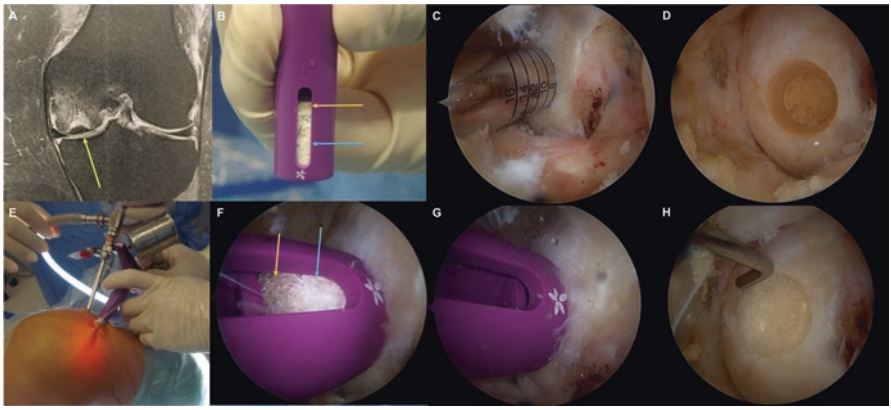

Fig. 2.2 Medial condyle unstable osteochondral defect (yellow arrow) (**A**), bilayered acellular scaffold with cartilage layer (orange arrow) and bone layer (blue arrow) (**B**), arthroscopy view with removal of the defect and preparing the receptor bone bed by means of a trephine (**C**), final arthroscopic look of the receptor zone (**D**), outside view of arthroscopic surgery (**E**), introduction of the acellular scaffold, (**H**) final aspect and palpation with a probe of the press-fit scaffold (**F**, **G**)

given the fact that it aims to preserve the native tissue. This is achieved by lifting the fragment (if possible keeping some partial attachment), preparing the bony beds from both sides (e.g., microfracturing) and fixation with screws or arrows [31]. Arthroscopic debridement and lavage with bone marrow stimulation such as drilling [62], microfracture (promoted by Steadman) [63], abrasion arthroplasty [64], and chondroplasty [65] are the initial surgical strategies. The rationale supporting bone marrow stimulation techniques is that by perforation of the subchondral bone, we create channels enabling the recruitment/migration of blood with growth factors and bone marrow stem cells to the defect site and formation of a stable clot, which fills the chondral defect [66–68]. Good short-term outcomes have been reported with this technique [69, 70]. Concerning histology, this treatment does not provide hyaline cartilage restoration [71, 72]. This healing process leads to fibrocartilage tissue formation, which has lower biomechanical characteristics and is more likely to break down [63, 73]. This relevant drawback is the main reason for the failure [63, 73]. Deterioration of clinical outcomes at long-term has been described, with revision surgery needed in some cases [74, 75]. Considering this fact, enhanced microfractures techniques have been recently developed with promising short-term outcomes [76–78].

More complex and anatomic strategies have been developed such as autologous or allogeneic osteochondral grafting, i.e., mosaicplasty technique [79]. Mosaicplasty is being used since 1994 when it was first performed by L. Hangody [80]. The OATS technique is used to transfer autologous (or allogeneic) bone and hyaline cartilage to the defect, providing a stable size-matched osteochondral autograft. For smaller defects, one single plug transfer to fill the defect seems to have advantages over several cylinders [79]. However, for larger defects, the mosaicplasty requires

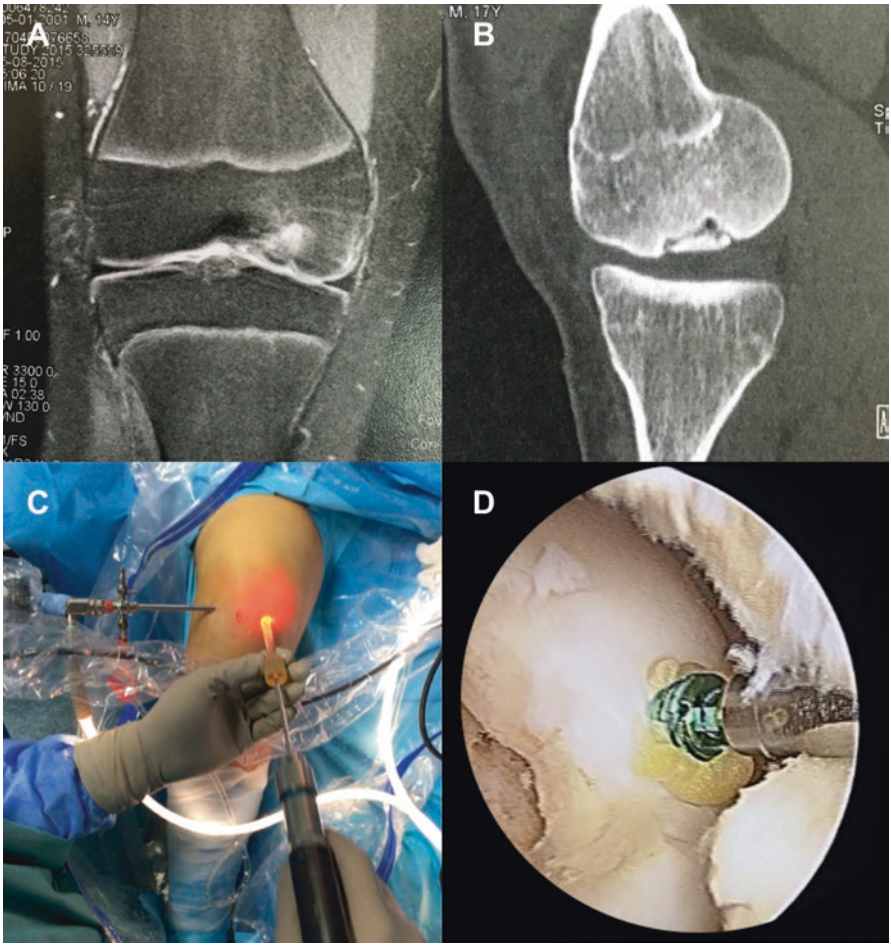

Fig. 2.3 MRI frontal view of medial condyle unstable osteochondral defect (OCD) with edema around the injury on T2 (**A**), CT lateral view assessing the underlying bone of the defect (**B**), outside view of the arthroscopic surgery (**C**), and OCD fixation with headless compression screw (**D**)

the transfer of multiple small cylinders (osteochondral plugs) to the defect [66, 67]. Nevertheless, this technique has several limitations such as restricted graft disposal and donor site-related morbidity once it creates a defect elsewhere in order to transfer tissue to the defect [81, 82]. Aiming to lower donor site morbidity, the upper tibiofemoral joint has been proposed as a potential donor site [79]. Despite its inherent risks and limitations, transplantation of osteochondral allograft is a viable option to manage larger osteochondral injuries, including those that involve an entire compartment [66, 67, 83].

The ACI approach (promoted by Mats Brittberg) is a two-stage procedure which involves harvesting of autologous chondrocytes on a first procedure, processing

these in laboratory, and latterly implanting these cells in the articular cartilage defect aiming to achieve hyaline-like cartilage repair [66, 67, 84–86]. This procedure expected to accomplish higher longevity of the healed tissue improves long-term clinical and functional outcomes [86, 87]. The initial technique required a periosteal flap to cover the defect (sutured to the surrounding cartilage), and the cells were finally delivered under this coverage with a small needle. However, consistently reproducible results favoring this technique over the others have not been achieved [60, 86].

As a more advanced tissue engineering and regenerative medicine (TERM) approach, the MACI technique is an attractive alternative which involves culturing the chondrocyte cells into a tridimensional porous scaffold which is matured in the laboratory by means of bioreactors and afterward implanted into the defect [66, 67]. The MACI technique is technically less demanding and reduces surgical time, besides avoiding periosteal harvesting [88]. The reported short-to-midterm outcomes show promising results of this technique in articular cartilage injuries of the knee joint [89–91]. However, using the same principle, stem cells combined with scaffolds (MASI) have been attempted in order to improve the achieved outcome and are under development and research [60]. Some of these TERM-based approaches have been made commercially available or under commercial advertising (Table 2.1). These new techniques aim to be potential efficient options to restore OCDs; however, there is still a lack of evidence-based medicine supporting its widespread use. In the authors' opinion, it should be kept under strict research control until further conclusions can be obtained. Some of these emerging techniques include autologous matrix-induced chondrogenesis (AMIC™) [92, 93], bone marrow aspirate concentrate (BMAC) and mesenchymal stem cell-induced chondrogenesis (MCIC™) [94–96], autologous collagen-induced chondrogenesis (ACIC™) [97, 98], minced cartilage repair (DeNovo NT and CAIS) [99–101], osteochondral biomimetic scaffolds (MaioRegen®) [102–105], and hydrogels acting alone or as carriers of cells and/or proteins (BST-CarGel®) [106–109].

Correction of malalignment or unloading of an affected compartment by means of the osteotomy (Fig. 2.4) (distal femur or proximal tibia) might favor the biomechanical environment around OCD or unicompartmental OA [110, 111]. Partial or total knee replacement by means of arthroplasty or even fusion in salvage procedures is considered as the last resource [38]. Prompt diagnosis and treatment of symptomatic OCDs have enabled better clinical outcome [86, 112, 113]. Moreover, several authors advise that early treatment diminishes the risk for additional cartilage degeneration and development of secondary knee OA [9, 14, 25, 62, 86, 112]. Based on current knowledge, the treatment of OCDs relies on the defect's size, the involvement of the entire osteochondral unit, and the time from injury to repair [114]. Many algorithms for treatment have been proposed [52, 114–119].

Table 2.1 Commercial available cartilage repair systems

Product name	Main material	Trials
ACI procedures		
ChondroCelect® TiGenix, Leuven, Belgium	10,000 cells/µl suspension (Dulbecco's modified eagles medium)	First approved cell-based product in Europe
Carticel® Genzyme Biosurgery, Cambridge, MA	12 million cells suspension	First FDA-approved cell therapy product
Chondro-Gide® Geistlich Biomaterials, Wolhusen, Switzerland	Collagen	Improved clinical outcome associated to MF or as an ACI procedure
MACI® Genzyme Biosurgery, Cambridge, MA	Porcine type I/III collagen	Phase III trials Improved outcome in case series in comparison with OAT and MF
CaReS® Ars Arthro, Esslingen, Germany	Rat-tail type I collagen	Improved clinical outcomes in a multicenter study with 116 patients/ follow-up: 30 months
NeoCart® Histogenics Corporation, Waltham, MA	Bovine type I collagen Chondrocyte culture in a bioreactor	Phase III trials
Hyalograft C® Fidia Advanced Biopolymers, Abano Terme, Italy	HYAFF 11-esterified derivative of hyaluronate	Improved clinical results even when compared with MF Improved clinical outcome in case series reported in 62 patients/ follow-up: 7 years
Cartipatch® Tissue Bank of France	Agarose-alginate	Phase III trials Improved clinical outcome in case series reported in 17 patients/ follow-up: 24 months
Bioseed C® BioTissue Technologies, GmbH, Freiburg, Germany	Copolymer of PGA, PLA, and PDS – fibrin glue	Phase III trial Improved clinical outcomes in in case series reported in 52 patient/ follow-up: 4 years
BioCart II ProChon BioTech Ltd., Ness Ziona, Israel	Fibrinogen + hyaluronan	Phase II trial Improved clinical results in case series reported in 31 patients/ follow-up: 17 months
DeNovo ET® Zimmer, Warsaw, Indiana	Matrix + allogenic fetal chondrocytes	Phase III trial
Cartsystem	Sodium hyaluronate + allogeneic umbilical cord MSCs	Phase II trial
Graft		
DeNovo NT® Zimmer, Warsaw, Indiana	Matrix + allogenic chondrocytes	Good clinical outcomes in few studies reported
CAIS® Depuy-Mitek, Raynham MA	Glue + autologous morcelleied cartilage	Phase III trial

(continued)

Table 2.1 (continued)

Product name	Main material	Trials
Cell-free scaffold		
TruFit® Smith & Nephew, Andover, MA	PLGA-calcium-sulfate biopolymer bilayer porous	Suspended commercialization
BST-CarGel® Biosyntech, Quebec, Canada	Chitosan + glycerol phosphate	Phase III trial Better outcomes than MF treatment in a 5-year follow-up
CaReS-1S® Arthro-Kinetics, Esslingen, Germany	Rat-tail type I collagen	Animal trials Short case series in adults
MaioRegen® Fin-Ceramica S.p.A., Faenza, Italy	Hydroxyapatite-collagen 3D tri-layers	Few studies

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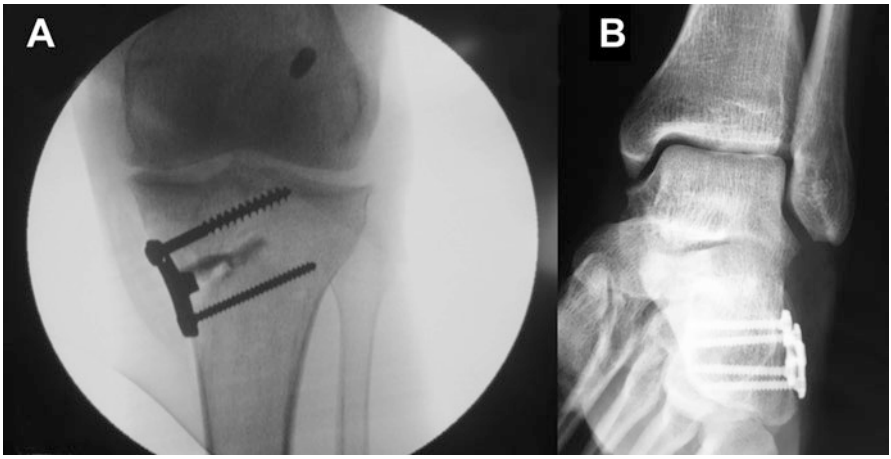

Fig. 2.4 Opening-wedge high tibial osteotomy of the knee (stereoscopy) (**A**) and calcaneal sliding osteotomy of the ankle (x-ray) (**B**)

2.5 Ankle Osteochondral Defects

An osteochondral defect (OCD) of the talus is a lesion involving the talus or distal tibia hyaline cartilage and its subchondral bone. Several classifications have been used over time, but the first comes from 1959 from Berndt and Harty [120]. The etiology of OCDs is often a single or repeated traumatic events [121]. However, ankle OCDs might also be idiopathic or non-traumatic [1, 121–123]. Similar to what happens for the knee joint, there is no single classification system, which fully

addresses the topic. The anatomical grid proposed by Raikin and Elias has proven its value by making it possible to describe the location and assist in a preoperative planning [124, 125].

Shearing forces might cause superficial cartilage lesions, without damage to the underlying subchondral plate. However, after a high-impact force or repeated trauma (chronic instability), the underlying bone plate can also be damaged [126]. Ankle trauma related to an OCD frequently progresses to the formation of subchondral bone cysts. These bone cysts, surrounded by nociceptors, cause recurrent deep ankle pain leading to functional limitation. Most OCDs of the talus are found on the anterolateral or posteromedial talar dome [127]. Lateral lesions are usually narrower and oval-shaped and usually are caused by a shear mechanism. On the other hand, medial lesions usually derive from torsional impaction and axial loading, so they are frequently deeper and more cup-shaped [1, 122]. Although an OCD can have an acute onset resulting from trauma, cystic degeneration is a slower process [128]. To date, there is still not a complete understanding of the etiology or the different clinical presentation and response to treatment of ankle OCDs, despite some valid theoretical explanations [1]. While some OCDs remain asymptomatic, others present fast degradation with cyst formation and bone edema [128]. If we could predict or understand the pathogenesis of such differences, we would most likely be more efficient in dealing with this condition. The clinical presentation of a symptomatic OCD is usually deep ankle pain aggravated by effort with recurrent swelling after activity [128].

Some type of trauma is frequently accepted as the principal etiologic factor of an OCD of the talus. Trauma has been implicated in 93–98% of lateral talar defects and 61–70% of medial OCDs [129]. Etiologic factors of an OCD can be traumatic or non-traumatic [1]. Other etiologic possibilities include vascular issues and genetics [122]. Furthermore, OCDs have been found in identical twins and siblings [130] in support of the previous. Moreover, ankle OCDs are bilateral in 10% of patients [131]. Traumatic cartilage lesions of the ankle can be divided as microdamage or blunt trauma, chondral fractures (sparing the underlying bone), and osteochondral fractures [132].

Ankle sprains or chronic ankle instability is an important cause of traumatic ankle OCDs [133]. This seems to be the most frequent cause of these conditions. When the talus is inverted between the tibial plafond, medial and lateral malleoli linked by syndesmotic ligaments (the ankle mortice), the cartilage of the talus can be crushed/fractured (causing a loose body) and cause a cartilage crack or delamination, or an underlying bone bruise. Shearing forces might cause separation in the superficial layer of the cartilage [1]. OCDs might remain stable or become unstable which aggravates progression to further joint damage [1]. In testing conditions, it has been possible to reproduce lateral ankle OCD defects by intensely inverting a dorsiflexed ankle (while the foot is inverted, the lateral border of the talar dome is smashed against the fibula while the lateral ligament is ruptured). During application of excessive inverting force, the talus rotated laterally in the frontal plane within the mortise thus impacting and compressing the lateral talar margin against the articular surface of the fibula. This mechanism leads to a lateral talar OCD. A medial

lesion was reproduced by plantarflexing the ankle while applying slight anterior displacement of the talus on the tibia, inversion and internal rotation of the talus on the tibia [1, 120]. Considering the previous one can assume that the treatment of ankle OCD without management of chronic ankle instability is extremely difficult and prone to failure. For this reason, one major advance in the treatment of ankle OCDs has been the concomitant arthroscopic approach of cartilage defects and lateral ligament's repair [134].

2.6 State of the Art in the Treatment of Osteochondral Defects of the Ankle

Asymptomatic incidental findings of the ankle are not infrequent, including within athletic population [135]. As aforementioned, ankle OCDs are frequently secondary to trauma, usually a consequence of ankle sprains during sports or chronic ankle instability. The available treatment options are basically similar to those on the knee. Asymptomatic OCDs can be dealt conservatively: physiotherapy, medication, orthobiologics, periods of rest, or immobilization (e.g., orthoses or walker boot) [121, 127]. However, we advise for surveillance of such injuries. Presently, there is no evidence-based or consensus in the literature concerning the superiority of any surgical treatment over another either in primary or secondary ankle OCDs [127, 136]. The final therapeutic decision relies on the patient profile and expectations as well as some characteristics of the lesion.

Preoperative planning is critical and should always include weight-bearing x-rays for alignment evaluation and global joint assessment. MRI can overestimate the size of the OCD by the presence of bone edema (usually reflects local biological activity, mostly visible in T2 sequences) surrounding the injury. The CT provides a more reliable assessment of bony defect size and volume. Additionally, CT on lateral view in plantar flexion or dorsiflexion is helpful to decide for the most advantageous anterior or posterior arthroscopic approach in a given case or even if an open approach is required (medial malleolar osteotomy for medial defects or lateral ligament detachment and afterward reinsertion for lateral defects). The arthroscopic approach is currently the preferred and most frequently used for both anterior and posterior compartments [137]. The authors advise for not using fixed distraction once this lowers the percentage of complications [138]. Moreover, as aforementioned, arthroscopy enables simultaneous treatment of concomitant pathologies (including instability) whenever required. Excision, curettage, and bone marrow stimulation techniques (ECBMS – excision of OCD fragment, curettage of subchondral bone with drilling or microfractures) aim to achieve fibrocartilaginous tissue formation which is still the less invasive surgical approach [136]. Satisfactory results with minimal aggression can be obtained depending on the patient profile and injury characteristics, and ECBMS can also be considered in bigger lesions

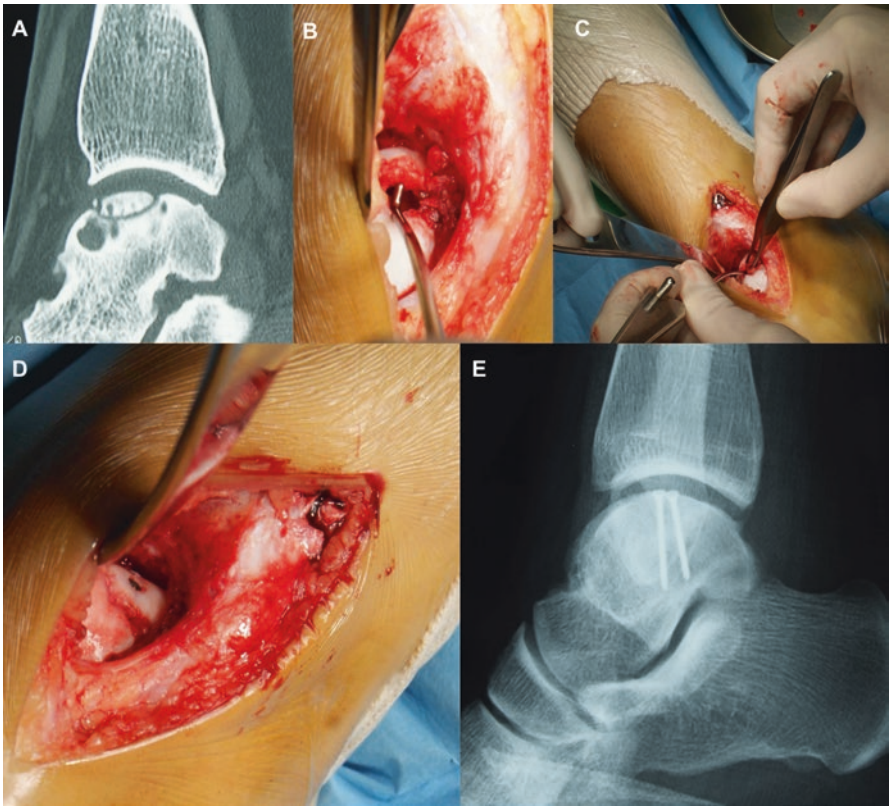

Fig. 2.5 Talar osteochondral defect with surrounding cystic lesions on CT (**A**), lifting of the defect on open surgery leaving partial attachment (**B**), filling of the defect with bone autograft after drilling (**C**), fixation of fragment with compression screw (**D**), and final x-ray look (**E**)

unable for fixation or even secondary injuries. ECBMS is considered in most cases given the outcome possibilities and lower aggression and cost. A lower percentage of good/excellent results is to be expected in larger lesions and revision surgery [136].

Preserving the native tissue by the "lift, drill, fill, and fix" surgery should be preferred whenever possible since it provides the preservation of the most of native tissue [139]. Lift the defect, drill by making microfracture or bone marrow stimulation, fill the defect with bone graft, and fix the fragment with metallic or bioabsorbable screws or pins (Fig. 2.5). This can be done fully arthroscopically in some cases or require open surgery on others. Retrograde drilling (Fig. 2.6) to decompress secondary cystic lesions linked to an OCD, and sometimes filling with bone graft, is a valid option for large cystic lesions [127]. OATS has some possible indications, but the high chance of complications must be acknowledged [82].

The osteochondral autologous transplantation surgery (OATS) technically (Fig. 2.7) is very similar to what is done in the knee joint. However, for most ankle lesions, it will require harvesting osteochondral cylinders from the knee to fill an

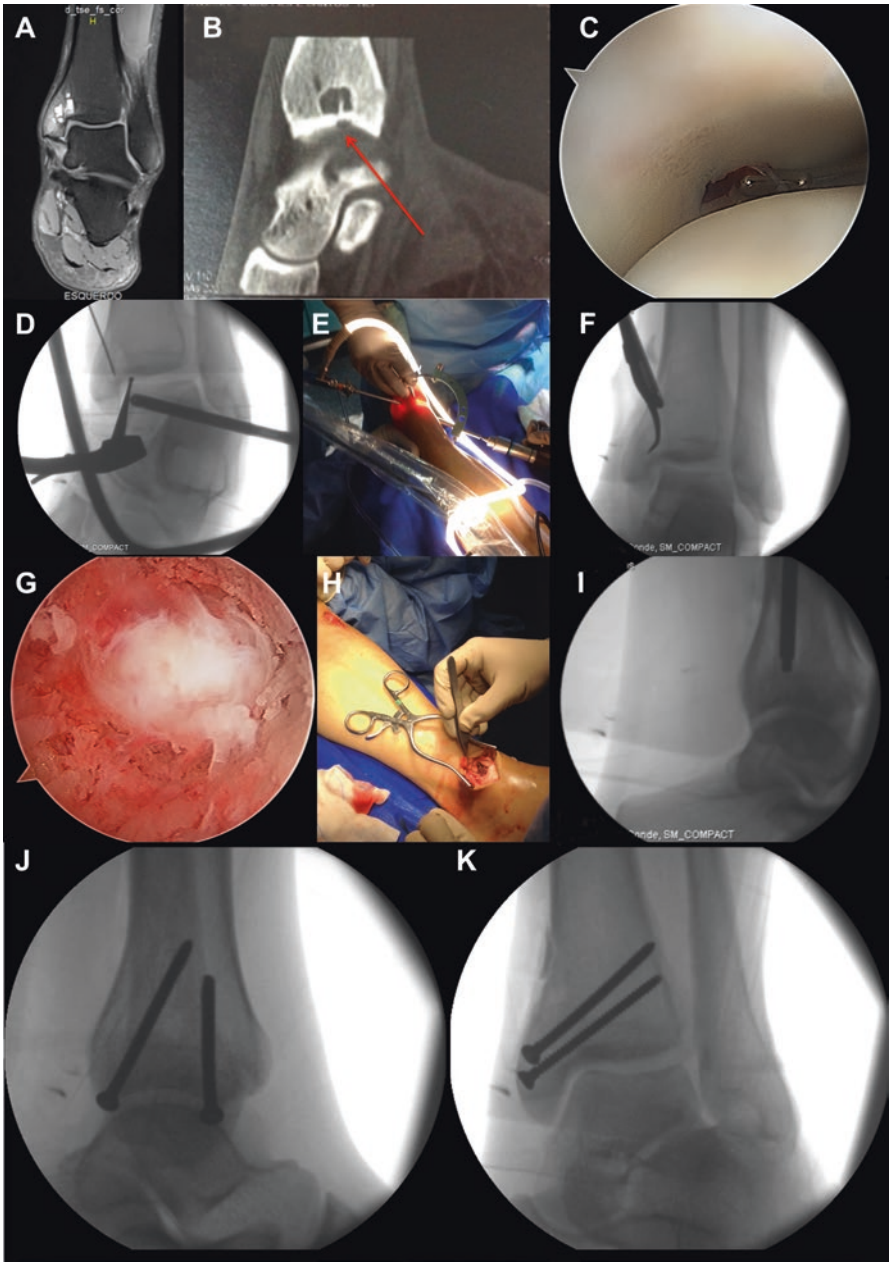

Fig. 2.6 Distal osteochondral defect (OCD) of medial malleolus – MRI view (**A**), CT view of the OCD with a small opening enabling fluid to get into the cyst (red arrow) (**B**), arthroscopic view of the cartilage small opening enabling fluid to get into the cyst (**C**), use of MicroVector guide for retrograde drilling to reach the defect under radioscopy control (**D**), outside view of the guide and drilling of a bone tunnel during arthroscopy (**E**), the arthroscope is introduced into the bone tunnel (osteoscopy) together with instruments for curettage of the cyst (**F**), inside view of the cyst from the arthroscope (**G**), bone autograft harvesting from distal tibia (**H**), the bone autograft is impacted into the defect (**I**), and two compression screws are included for extra support and compression to enhance healing (**J**, **K**)

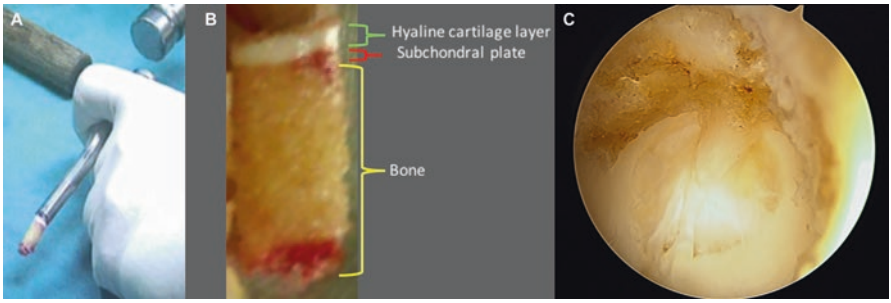

Fig. 2.7 After harvested, the osteochondral autograft is removed from the trephine used to collect it (**A**), aspect of the harvested autograft including fresh hyaline cartilage, subchondral bone and cancellous bone (**B**), arthroscopic view of a cylinder in place at 1-year follow-up (**C**)

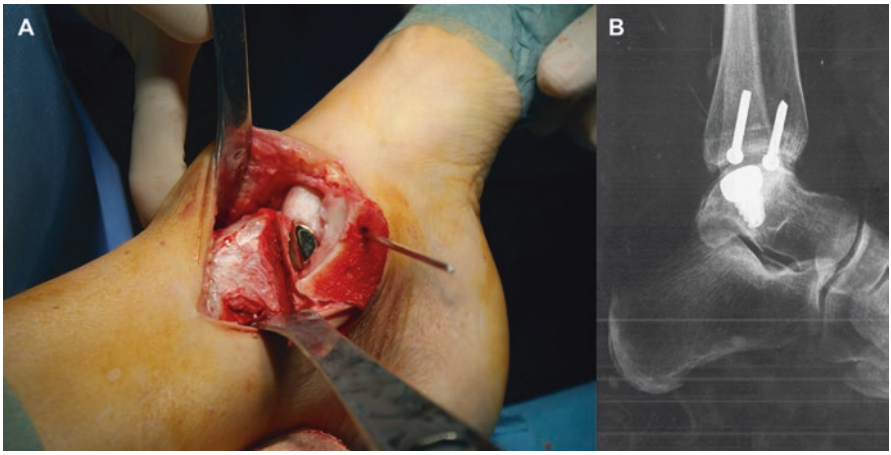

Fig. 2.8 Surgical view of the Hemicap® implant (**A**) and x-ray view of the implanted Hemicap® (**B**)

ankle defect. Although the promoters state high rate of a successful outcome, a systematic review has shown that this technique has a considerable amount of complications [82]. This must be considered by doctors and patients.

Tissue engineering and regenerative medicine (TERM) approaches promise a better and broader option for the future. However, similarly to what has been observed in the knee, cell-based therapies, scaffolds, and augmentation with hydrogels, despite very promising, so far, have not been able to provide consistently better results. Considering the former, and their higher cost, they are valid options for revision surgeries or large injuries without possibility for fixation and not amenable by any of the previous techniques, and as an approach to primary ankle OCD, we advise to keep this technology under research and controlled conditions before its extensive advertising [108, 109, 140–154]. When all biology-based surgical treatments fail, partial medial talar dome replacement by a metallic implant (Hemicap®) (Fig. 2.8) has provided positive midterm results [155]. Biomechanics remains a pillar of orthopedics. So improving the load distribution and joint

alignment by means of osteotomy has proven positive effects either isolated or in combination with other procedures [28, 156]. The goal is to unload the most affected part while distributing forces to the most preserved part of the joint. Ankle fusion or ankle arthroplasty represents the last resource when dealing with very symptomatic OCDs or ankle OA [28].

2.7 Joint Anatomy, Congruency, Alignment, and Osteochondral Lesions

There are important anatomic and biomechanical differences between the knee and ankle joints, which might help to enlighten some aspects related to pathophysiology and treatment. Opposing to the ankle, the knee joint has two menisci which function as fibrocartilaginous dampers (dispersers of load), which assist in compensation on the basic incongruence of the knee joint. Menisci help to adjust the incongruity between the tibial plateau and the femoral condyles. Moreover, they increase the articulating joint surfaces, consequently reducing the load on the entire joint surface.

Another aspect is that the cartilage thickness is quite different among them. The common cartilage thickness of the talus is 1–1.7 mm, while in the knee joint, it ranges from 1 to 6 mm, depending on the location [157]. Moreover, the mechanical properties including stiffness of the talar cartilage are much more constant in the main loading area, while in the knee joint, the cartilage's properties are much more heterogeneous [158].

At higher loads, the ankle becomes a fully congruent joint [158]. The ankle has a smaller contact area than the knee in loading conditions. The contact area in the ankle at 500 N axial load is 350 mm [159–161] compared to 1120 mm^2 in the knee [162]. Therefore, it might be concluded that the total load and the load peaks in the ankle are higher than in the knee due to the smaller contact areas and the lack of damping structures. The constant hydrostatic pressure within a congruent joint like the ankle causes a permanent fluid pressure toward the subchondral plate. When the cartilage envelope of the joint is interrupted due to cartilage lesion, hydrostatic pressure might lead to secondary osteolysis and cyst formation (Fig. 2.9) [1].

The anatomical features, as well as the biomechanical differences alone, fail to explain the higher frequency of OA of the knee. Among the factors that lead to the onset and progression of OA, traumatic injuries of joint structures, as they occur in intra-articular fractures, have a critical role. A traumatic injury to the articular surface results in an immediate loss of biological features and biomechanical function [1]. A biochemical damage also occurs after trauma with loss of matrix components which might influence the risk of OA [163]. Sprains of the knee and ankle joints are among the most common injuries in sports. This can cause ligament injuries, meniscus tears (in the knee), and cartilage and bone lesions with varying degrees of severity which might be implicated in cartilage damage and OA risk.

Osteotomy is a surgery in which the bones are cut and their alignment changed with subsequent biomechanical implications in all joints. Osteotomy around the knee

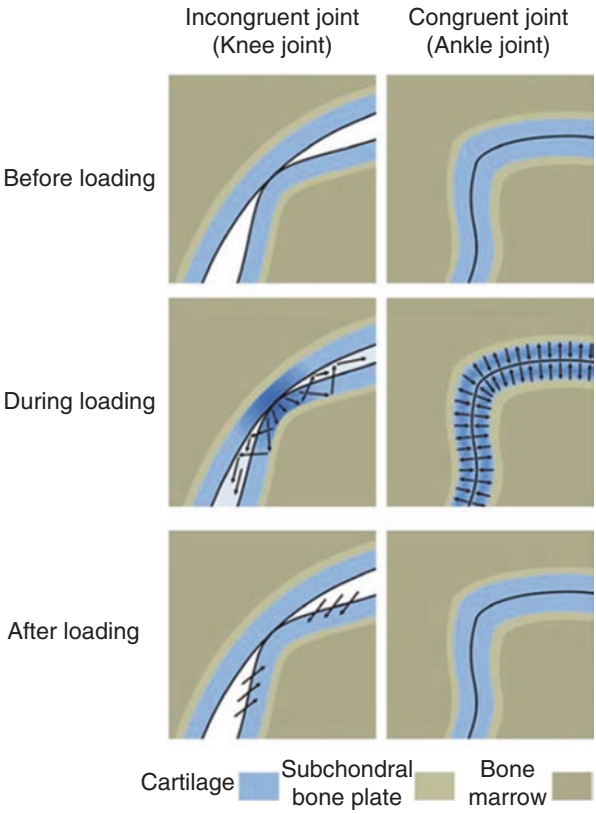

Fig. 2.9 Schematic comparison of the deformation of the cartilage in a congruent (ankle) and incongruent (knee) joint before, during, and after loading. Arrows = direction of water. (Reproduced from van Dijk et al. [1])

alters the alignment of the knee. Weight bearing will be shifted from the affected segment to a healthier part of the knee. By "unloading" the damaged cartilage, osteotomy may decrease pain, improve function, slow the joint degeneration, and possibly avoid or delay the need for (partial or) total knee replacement surgery [111].

Despite some methodological limitations on the available literature, it has been shown that valgus high tibial osteotomy reduces pain and improves function in patients with medial compartmental osteoarthritis of the knee [111]. So far, the results do not justify a conclusion on the benefit of any specific high tibial osteotomy technique for knee osteoarthritis over another [111].

Corrective ankle osteotomies enroll periarticular osteotomies of either the fibula, distal tibial metaphysis, or distal tibial metaphyseal-diaphyseal junction. Osteotomies are indicated under the presence of angular, rotational, or translational malalignment [164, 165]. Various types of realignment surgery are employed to preserve the ankle joint in cases of intermediate ankle arthritis with a partial joint space narrowing. Promising results considering pain, function, and imaging have been reported [165]. In conclusion, improvement of biomechanical environment might be helpful alone or in combination with any other "biological" treatment in either knee or ankle joints.

2.8 Current and Future Perspectives

2.8.1 Injections and Other Therapies with Growth Factors and/or Stem Cells

The orthobiologics approach, including anabolic proteins (growth factors (GFs)) [148, 166–168] and mesenchymal stem cells (MSCs) [144, 154, 167, 169–175] with or without hydrogels (e.g., hyaluronic acid, collagen, chitosan-based) [140, 150, 176–181], represents a step forward on conservative or minimally invasive therapy of both OCDs and OA.

The capacity for tissue repair is influenced by GFs, which have functions like chemotaxis, cell differentiation, proliferation, and cellular responses, which may potentially improve tissue healing (including the cartilage and bone). Therefore, the use of autologous and recombinant GFs is evolving in several fields of orthopedics. However, we need to fine-tune this technology in order to have adequate GFs acting in each tissue in proper time. As an example, platelet-rich plasma (PRP), a source of a cocktail of several autologous GFs, cannot be all things to all tissues. PRP is obtained from patient's own blood (autologous), and GFs from alpha granules of platelets become available after the platelet activation procedure. The next step will be to customize PRP for specific indications, an innovative and potentially rewarding concept [182]. The goal is to manipulate GFs and secretory proteins aiming for both cartilage and bone repair at the same time for an OCD. Many questions remain to be answered, including therapy timing (when to start therapy, how many applications, and for how long); which type of preparation, volume, or dose; and frequency of treatment [182–184]. It is difficult to compare clinical outcome PRP since there are many different methods for preparation that provide different products, for instance, regarding the GF and leukocyte concentration [168, 185].

The most widely used GFs are bone morphogenetic proteins (BMPs) and PRP [145, 167, 172]. GFs can also be genetically modified to improve its function or even use gene therapy to increase expression of a specific GF if needed for tissue healing [145, 186]. Another promising field is the use of stem cell-based therapies. Mesenchymal stem cells (MSCs) have differentiation competence for mesodermal lineages [187]. The modulation of adult MSC pathways can lead to chondro-, osteo-, and adipogenesis (chondrocytes, osteoblasts, and adipocytes, respectively) [188, 189]. The therapeutic possibilities of their use are extraordinary.

MSCs can be isolated from different tissues such as the bone marrow, skin, fat, synovia, and muscles, or from aspirates such as the bone marrow, adipose-derived [95, 169, 190–192]. MSCs allow its transplantation without provoking an immune response [193]. Depending on its source, MSCs show different performances. Bone marrow stem cells are still the most studied ones [194]. Bone marrow aspirates from the iliac crest have been used to treat chondral lesions and OCDs [195–198]. After harvesting by means of aspiration, MSCs might either be submitted to laboratory expansion within 2–3 weeks for subsequent use or the aspirate itself after concentration (centrifugation) can be immediately implanted. Moreover, in

advanced TERM strategies, they might be combined with GFs, platelet-rich fibrin gel [95, 197, 199–201], fibrin glue [196] collagen gel [195, 196, 199, 200, 202] or collagen [95, 195, 196, 203] and HA [197, 199, 200, 202] scaffolds, among others [60, 204].

MSC-based treatment of focal chondral lesions and OCDs has shown promising clinical outcome in both the knee [95, 196, 197, 203, 205–208] and ankle [199, 200, 202] joints. Some reports of hyaline cartilage repair have been recently presented [209]. Moreover, a cryopreserved form of human amniotic membrane and umbilical cord (hAMUC) fetal tissues has been proposed for osteochondral injuries. These tissues have unique proteins and growth factors in the extracellular matrix and have shown to modulate inflammation, reducing adhesion and scar formation while encouraging regenerative healing [210]. Despite the very limited clinical experience, this possibility is under commercial promotion already (Amniox®). Hydrogels function by their own properties (rheological, anti-inflammatory, lubrication), but they may also function in combination of GS and/or MSCs as well as promising scaffolds which might also enable control of neovascularization process (of particular relevance concerning hyaline cartilage) [150, 177–181]

2.8.2 Tissue Engineering and Regenerative Medicine Approaches

The combination of the TERM triad (cells, scaffolds, and GFs) despite remaining a challenge is still the main goal in any tissue repair [209, 211–214]. Moreover, the possibility of one-step procedures for full OCD repair remains a major goal to fasten recovery process and avoid comorbidity and costs. Such approach has been attempted with some success [195, 199, 215, 216]. Giannini et al. [199] combined BMC and PRP gel with HA membrane or collagen powder to treat talar OCDs with positive short-term results. Moreover, histological biopsies have shown hyaline-like cartilage [199, 216].

The use of multilayered scaffolds facilitates the regeneration of the native tissue with hyaline cartilage and subchondral bone [103, 153, 204, 209, 217–221]. However, in respect for biology and the complex chain of events leading to tissue repair, enhancing scaffolds with cells and/or growth factors seems theoretically more promising in any tissue as suggested by clinical and basic science research [214, 221, 222]. The final goal of TERM [211, 223] is to develop an effective scaffold that is seeded with suitable cells and growth factors and matured in the laboratory with the use of bioreactors, and accomplishing a tissue that would be suitable for clinical implantation with similar characteristics to the native one.

Nanotechnology seems a promising field once we can use nanoparticles to deliver proteins and/or cells in different layers of a given scaffold aiming to influence the healing of different tissues according to its needs [217, 224, 225]. Moreover, it enables to label stem cells and influences their behavior in the biologic environment

[226]. Similarly, this can be used for bioactive proteins [227–229]. Besides, some authors suggest that nanoscale fibrous scaffold architecture is crucial in promoting and maintaining chondrogenic differentiation [230].

A multilayered collagen-based scaffold has been developed including the use of hydroxyapatite nanoparticles, which might enhance bone integration [103]. Another silk-based nanofibrous and nanocomposite bilayer scaffold used calcium-phosphate nanoparticles [217]. Some authors proposed bilayer scaffolds including microspheres with TGF-β for chondrogenic differentiation and BMP-2 for osteogenic differentiation [231], and several other improvements are under development [232]. Moreover, the combination of specific hydrogels or even gene therapy [233] can further enhance this process for future clinical use [153, 179, 234]. Another very promising possibility for TERM approaches is the possibility for three-dimensional (3D) bioprinting techniques which enable to fabricate injury-specific implants [235–238]. This is particularly helpful in the geometrically difficult parts of joints. 3D bioprinting can be used to produce custom-made, regenerative constructs for tissue repair [237]. 3D bioprinting techniques permit incorporation of cells and bioactive molecules during the fabrication process in order to create biologically active implants [237]. The outer shape of the construct can be made accordingly to the patient's defect based on CT and/or MRI images of the lesion. Moreover, it enables to achieve more complex zonally organized osteochondral constructs by printing with multiple bio-inks [237]. A large number of possibilities exist including hybrid printing such as thermoplastic polymers and hydrogels or incorporation of electrospun meshes in hydrogels, nanoparticles with cells, and/or bioactive molecules to optimize biomechanical and biological capacities of the construct [237].

2.9 Final Remarks

Cartilage or osteochondral defects are very frequent injuries affecting millions of people worldwide. Development of osteoarthritis (OA) is a relevant socioeconomic burden, which requires more effective possibilities for treatment. OA is more frequent in the knee than in the ankle. Most ankle OCDs are linked with the consequence of traumatic events and ankle sprains (which is one of the most frequent injuries in sports). The knee and ankle have different biological and biomechanical features, which help to understand some differences in physiopathology and response to treatment. However, a lot of further research is required in this setting. Conservative treatment remains the first option in treatment in most OCDs or OA. In this field, the development of orthobiologics (injectable hydrogels, growth factors, cell-based therapies, and so forth) has provided new options for some patients. Concerning surgical treatment, technical developments have been improving the outcome of classical approaches such as bone marrow stimulation techniques. Autologous osteochondral transplantation, despite remaining a valid option, has been linked with the significant amount of complications, which must be acknowledged. The first generation of autologous

chondrocyte transplantation has not achieved the expected results. The use of acellular scaffolds has been under intense research and development. The combination and use of cells, growth factors, and cells in advanced TERM approaches promise to improve future outcome. Joint realignment by means of osteotomies is also a valid surgical tool, both in the knee and the ankle. Joint replacement offers many different possibilities including partial replacement. Results of different techniques are not the same in the knee and the ankle, which seem to be multifactorial. The road for the future will upraise most probably from TERM approaches including gene therapy, nanotechnology, and custom-made implants.

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