OSTEOCHONDRAL INJURY OF THE KNEE, MANAGEMENT TECHNIQUE AND FUTURE DIRECTION

Abstract

Worldwide for orthopedic surgeons; osteochondral injuries are a common clinical issue. Injury to the chondral and osteochondral structures is widespread and mainly affects an active, young population. The onset of articular cartilage abnormalities that result in higher joint contact pressures, more joint degeneration, and possibly the development of osteoarthritis follows the initial step of these alterations, which is a loss of cartilage volume and function (chondropenia). For assessing chondral and osteochondral injuries, MRI is becoming more and more significant. The initial line of treatment for an osteochondral lesion should always be fixation in the event of a big acute osteochondral bone. Autologus and allogenic graft possibilities may be used by a surgeon if more donor tissue is needed. More contemporary cell culture approaches (cells and growth factors) have been researched with the goal of altering the cell microenvironment to promote cell differentiation and provide regenerative capacity.

Keywords: Osteochondral injuries, Osteochondral allograft, Subchondral bone, Stem cells

Authors

Dr. Narendra Singh Kushwaha
Additional Professor,
Department of Orthopaedic Surgery
King George Medical University
Lucknow, India
nskortho@gmail.com

Dr. Puneet Kumar
Associate Professor
Department of Rheumatology
King George Medical University
Lucknow, India

Dr. Rajat Kapoor
Assistant Professor
Department of Orthopaedics
S.N. Medical College
Agra, India
rajatsarvkapoor@gmail.com

Dr. Ashutosh Verma
Senior Resident
Department of Orthopaedic Surgery
King George Medical University
Lucknow, India
glamourashu5856@gmail.com

Dr. Atul Kumar Saroj
Senior Resident
Department of Orthopaedic Surgery
King George Medical University
Lucknow, India
atul.saroj19@gmail.com

I. INTRODUCTION

Osteochondral injuries of the knee are abnormalities of the cartilage surface and subchondral bone, most usually traumatic in nature[1]. However, it can be linked to a number of clinical conditions, from osteonecrosis to trauma. Osteochondral injuries are distinguished from chondral lesions in that they affect both the chondral surface and the subchondral bone, makes treatment more difficult than in the case of a chondral injury that occurs in alone. When marrow components are able to contact the defect site due to subchondral bone involvement, the body is able to respond naturally to the injury. The second distinguishing characteristic of osteochondral injuries is that the physical strength and nutritive support of the chondral joint surface are compromised by injury to the subchondral bone. Due to the poor blood supply to this region of the body, injuries don't always heal as quickly.

In a prospective and retrospective analysis of more than 31,000 knee arthroscopies, **Curl et al.**[2] found that 63% of patients had grade III or grade IV lesions in their articular cartilage. Disability may develop over time if these injuries are not addressed. The knee is susceptible to a variety of osteochondral injuries due to the forces exerted during athletic training. It is necessary to understand how osteochondral status affects limb straightening, meniscus and ligament status in the event of injury. A short-term drop in athletic performance may result from a weakness in one component of this functional unit, which may also affect the other components. A decrease in athletic performance may be accompanied by the onset of chondropenia and, eventually, osteoarthritis if articular cartilage loses its capacity to adapt to repeated stress. The etiology of osteochondral injury, the functional elements of articular cartilage, the clinical assessment and treatment of athletes with osteochondral knee injuries are all covered in this chapter.

II. CAUSE AND CLINICAL PRESENTATION

1. Mostly Osteochondral Injuries are Caused by one of two Events

- Wear and tear over the time
- Injury from sport activity or trauma- it usually occurs with a combination of twisting force and impact that damages the cartilage.

2. When Osteochondral injury is present, they can present with pain, limited movement and problems in daily activity. Pain can range in their severity:

- **Mild Pain:** caused by cartilage damage
- **Moderate Pain:** caused by fragment of bone and cartilage
- **Severe Pain:** due to total loss of cartilage, leaves bones grinding together

III. ANATOMY OF SUBCHONDRAL BONE AND ARTICULAR CARTILAGE

A deeper subchondral bone component and an articular chondral component form the osteochondral unit[3]. Articular (or hyaline) cartilage is a viscoelastic substance that permits the knee to tolerate varying loads during regular activities and sporting activities. Performing this function requires reducing friction on the articular surface and stress on the subchondral bone. Articular cartilage creates joint surfaces of less friction and wear, essential for easy range of motion.

A most important part of the osteochondral unit is the osteochondral junction that facilitates connection between the upper chondral surface and the lower subchondral bone. It controls nutrients exchange, mineralization and differentiation chondrocyte cell subtypes. The layer of calcified cartilage, which connects to the subchondral bone, has chondrocytes enclosed in a mineralized ECM. These characteristics contribute to its high stiffness, which helps to bind articular cartilage to underlying subchondral bone[4].

The subchondral bone, which is made of dense, non-permeable bone with numerous penetrating vascular canals, strengthens and nourishes the tissues above it. Trabecular bone, which makes up the deeper layers of the subchondral bone, can disperse and sooth forces applied to the joint[5]. The multiple distinct functions of each layer of the osteochondral surface are summarized in Figure 1.

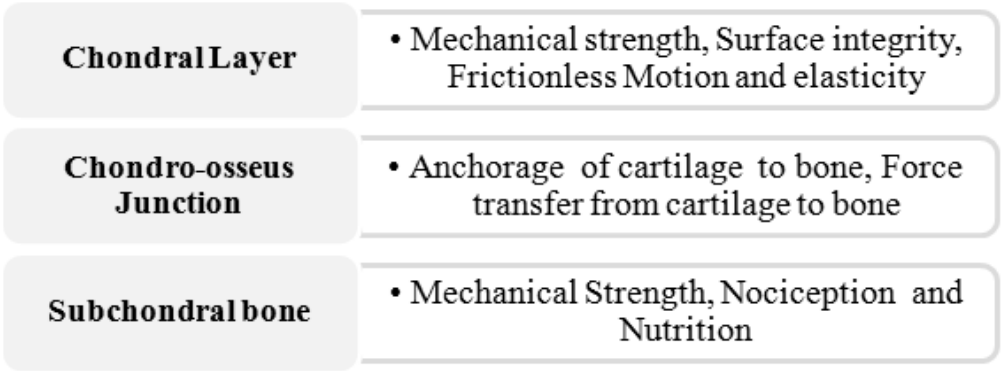

Figure 1: Components of subchondral unit and their functions

IV. PATHOPHYSIOLOGY OF AN OSTEOCHONDRAL INJURY

1. **Chondral Integrity is Progressively Lost:** Despite the fact that the native course of chondral damage in the knee is not properly described, it is clear that aging, pathologic loading, and articular damage can all lead to a loss of articular integrity. This loss can eventually lead to degenerative changes. A dose-response curve can be used to clinically represent the continuum of cartilage injury (Figure 1). The articular cartilage receives a force (dose) when the competitor competes. A common response happens if the cartilage is healthy. The ultrastructural characteristics of articular cartilage, however, are no longer able to respond adequately when chondropenia and articular cartilage abnormalities progress, resulting in feelings of discomfort, edema, and a decline in athletic performance.

2. **Spectrum of Athletic Injury:** The subchondral bone beneath the articular cartilage is unaffected by focal cartilage lesions, which solely affect the articular cartilage. These lesions might have partial or complete thickness. Lesions that are only partially thick do not penetrate the tidemark and cannot heal. Although reaching the subchondral bone, full-thickness lesions do not penetrate the tidemark (Figure 2). To make it easier to describe and track the clinical progression of chondral pathology, there are two classification schemes available. Six unique arthroscopic appearances were identified in the authors' examination of chondral damage of the distal femur, which served as the basis for the Bauer and Jackson classification system (Figure 2).

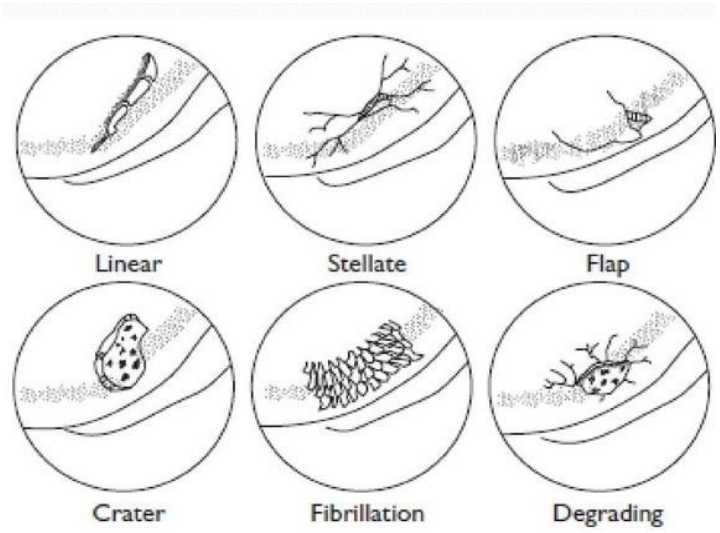

Figure 2: Chondral lesions of the femoral condyle are classified by Bauer and Jackson[6]

The updated International Cartilage Repair Society (ICRS) articular cartilage damage grading system is primarily based on the degree and depth of chondral disease (Table 1)[7]. Pain, edema, and athletic dysfunction are symptoms of localized chondral lesions. Patients frequently have symptoms that are identical to meniscal injury, making chondral lesions difficult to diagnose. Focal chondral lesions' natural course is still unknown. Deeper lesions tend to advance and enlarge over time as a result of stress concentrations along the margin of the hole.

Injury Grade Injury		Description
0		healthy cartilage
1	A	Soft dimpling
	B	Cracks and fissures on the surface
2		Defects that go down to less than 50% of the cartilage's depth
3	A	defects that go deeper than 50% of the cartilage
	B	defects that go all the way to the calcified layer
	C	defects that reach the subchondral bone but not through it
	D	Delamination
4		severely aberrant, with subchondral plate penetration

Table 1: Modified International Cartilage Repair Society Chondral Injury Grading System

3. **Osteochondral Fracture:** Due to the ability to identify the bone component on radiographs, osteochondral fractures are simpler to diagnose than chondral defects. Patellar dislocation frequently leads to osteochondral fractures. Osteochondral fractures have an unspecified natural history. The covering articular cartilage may eventually

deteriorate as a result of the initial traumatic event, yet the underlying bone can recover with anatomic reduction and solid fixation.

V. BIOMECHANICS

The osteochondral unit has several functions, with some overlapping and specialized functions played by each layer of tissue. The chondro-osseous junction divides the chondral and subchondral tissues, permitting them to work simultaneous to enable the complete osteochondral component meet its requirements to maintain the homeostasis of healthy joints[8]. The chondral layer must resist friction and shear stresses that are produced cyclically during normal joint articulation in addition to bearing vertical load, like the majority of the osteochondral unit. The best way to describe chondral tissue is as biphasic because it exhibited traits of both a fluid and solid phase component. Its solid phase is made up of ECM, its fluid phase is composed of water and inorganic ions like as sodium, potassium, calcium and chloride[9]. Due to the matrix's viscoelastic characteristic, the flow independent mechanism is facilitated[10, 11]. These mechanisms cause the chondral tissue to stiffen and become more force-resistant as the applied forces grow.

VI. DIAGNOSIS

Assessing a patient for chondral or osteochondral injury requires a thorough understanding of the functional unit of articular cartilage. The strain on the chondral surface will rise due to misalignment, meniscal integrity loss or ligamentous instability, which may exacerbate already-existing abnormalities or obstruct successful restoration or repair.

1. **History:** A precise and comprehensive history of patient is important. The history should include details on the traumatic event, as well as the kind, timing, location, and persistence of symptoms. The non-specific symptoms that patients typically report having include localized discomfort, edema and loss of motion. Mechanical catching may be used to describe a defect where a detachable or loose body is present.

2. **Physical Examination:** It is crucial to assess range of motion, edema (soft tissue, joint effusion), and joint line discomfort. Evaluation of the anterior and posterior cruciate ligaments, as well as varus or valgus malalignment, might reveal information about the macroenvironment of the knee and potential forces that could be transmitted through a cartilage defect. The asymptomatic side should be compared to each examination component. A gait analysis should be included of the examination to check for dynamic pathology and adaptive mechanisms that lessen the weight bearing on the joint. Wilson[12] described using a practical physical exam test to check for osteochondral injuries of the knee. The Wilson sign is produced by internally twisting the tibia while flexing the knee to 90 degrees, and then raising the knee gradually. A positive sign is pain that is alleviated by external tibial rotation at around 30 degrees of flexion.

3. **Imaging:** The weight-bearing anteroposterior, 45-degree flexion posteroanterior, patellofemoral, and lateral images make up the typical radiographic series. Other views include "long-leg" hip-to-ankle videos, which are used to evaluate the mechanical axis of the limb. The breadth of the joint space on weight-bearing radiographs has been used as a stand-in for cartilage integrity because cartilage cannot be detected on conventional

radiography. For assessing chondral and osteochondral injuries, MRI is becoming more and more significant (figure 3).

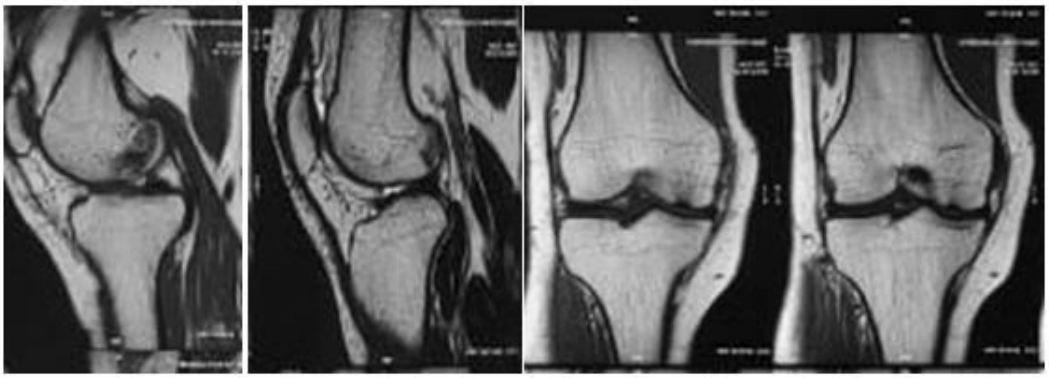

Figure 3: MRI finding showing subchondral injuries in both coronal and sagittal section

What constitutes the characteristic magnetic resonance appearance of articular cartilage is still a topic of debate among researchers today. Researchers have used a range of magnetic resonance pulse sequences to visualize articular cartilage and have come to a variety of findings on how it appears. Articular cartilage exhibits a multilaminar look on high-resolution MRIs. The number of layers and the histologic importance of each layer in normal articular cartilage are both subject to debate. Although MRI has advanced significantly over the past few years, plain radiography may no longer be necessary to evaluate the structure of the articular cartilage. The capacity of MRI to detect focal lesions is improved when contrast enhancement is used, either directly or indirectly by injection. A recent preliminary investigation showed a strong association between arthroscopic findings and cartilage damage quantification based on MRI. The assessment of chondropenia and osteoarthritis progression as well as MRI-based measurements of cartilage thickness and volume have all been studied by various researchers. For the evaluation of the severity of knee osteoarthritis using an MRI, interobserver agreement, predictability, and accuracy are still major issues. Also, the best imaging procedures have not been established. As a result, the potential of MRI or arthroscopic diagnosis (figure 4) as a main technique for measuring outcomes in osteoarthritis studies has not been fully realized.

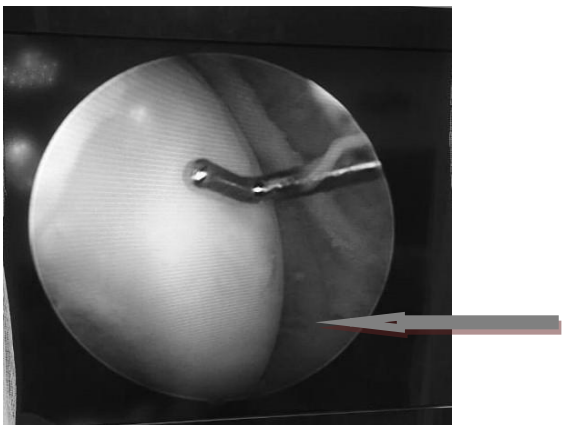

Figure 4: Arthroscopic finding showing subchondral injury

VII. REPAIR METHODS

1. **Fixation of Fractured Osteochondral Fragment:** A substantial bone fragment that can be reduced and repaired back into the site of the defect may be present within the joint in some acute traumatic osteochondral injuries. This typically relies on the length of time after the injury, the fragment's integrity and its size. There have been many fixing methods mentioned, including screws, metal or biodegradable pins, fibrin glue, and sutures. Each technique has been shown to produce satisfactory osteochondral fragment union rates, but there are drawbacks and issues with each approach[13], include tissue responses, delayed deterioration, and subchondral re-modelling, as well as the requirement to remove the second stage implant[14]. The goal of newer suture techniques is to lessen the need for implant removal, tissue response, and implant footprint[15].

2. **Osteochondral Autologous Grafting:** Osteochondral autograft grafting has become more common since it was first introduced by **Matsusue et al.** (1993)[16]. A cylindrical plug is utilized in this surgery to remove both the subchondral bone and healthy articular cartilage. This is frequently carried out from the area of the femoral trochlea that does not bear weight. This cylinder's smooth, healthy, mature hyaline cartilage can be used for the repair because its components fit the lesion site. The process can also be carried out using a mosaic of cylinders, each with a smaller diameter. In knee joint preservation surgery, autologus grafting, particularly in lesions smaller than 2 cm^2, has shown encouraging clinical outcomes and long-term outcomes[17, 18]. Allogeneic graft possibilities may be used by a surgeon if more donor tissue is needed.

3. **Implantation of an Osteochondral Allograft:** Osteochondral allograft implantation (OCI), a well-known surgery where an allograft is used for lesion restoration, is used to treat larger osteochondral lesions. This provides all of the benefits of OCI with the added bonus of having low donor site morbidity. The subchondral and bony component, however, cannot be said to do so because it does result in a considerable immune response that intensifies with the size of the graft tissue[19]. Younger, more energetic patients have had better success with OCI transplantation, where patient selection is crucial[21]. The prognosis of OCI is significantly influenced by factors like age, sex, body mass index, and overall degree of physical fitness[21]. When marrow stimulation has been found to produce suboptimal outcomes, OCI can be utilized for lesions larger than 2 cm^2. OCI and cell-based treatments are alternatives for areas larger than 2 cm^2, but neither one addresses the diseases of the subchondral bone, and both have negative donor site effects. OCI is therefore recommended for lesions larger than 2 cm^2 in cases when there is a lack of or insufficiency of autologous donor tissue.

VIII. REGENERATIVE TECHNIQUE

1. **Cells:** Bioactivity is required for a regenerative osteochondral implant, as was already mentioned, and the inclusion of cells is the single most important factor in making it so. Several cell sources, including embryonic stem cells (ESCs) and MSCs, have been researched and used. Given the ethical challenges ESCs face, mesenchymal stem cells (MSCs) have remained more popular[22]. MSCs have been found to originate from a range of tissues, including bone marrow[23], adipose[24], synovium[25], periosteum[26] and muscle[27]. Recently found induced pluripotent stem cells (iPS cells) are more widely accessible cell

sources with enhanced differentiation and proliferation potential[28]. Embryonic and induced pluripotent stem cells can differentiate into any of the three germ layers and have unrestricted proliferation capacity, which raises the possibility of teratoma formation[29]. Each MSC source has unique benefits and drawbacks. While bone is excellent for the osteochondral unit, adipose tissue has shown to have the best yield for cell number extraction. Although though synovium has been shown to have the best capacity for osteogenic and chondrogenic development when compared to bone marrow and adipose tissue, when used in clinical applications, it must be extended[30]. Since that in vitro multiplication has been demonstrated to have detrimental effects on cell homing, the high MSC output in adipose tissue is advantageous[31]. With many strategies now being explored, cells have been combined with tissue engineering for osteochondral regeneration. In the past, an autologous biopsy using the patient's own chondrocytes and osteoblasts during acute chondral injury was the most popular form of treatment. However, this did not produce enough cell numbers. MSC therapies that do not require an autologous articular cartilage biopsy have the advantage of using pluripotent MSCs, which are distinct from previously differentiated chondrocytes. The main benefit of employing MSCs is that they are bioactive, which allows for improved body integration and the ability to effectively impact and mediate biological processes.

2. **Growth Factors:** The most biologically active component of a regeneration process is growth factors. They direct and start a variety of cellular processes that promote chondrogenesis and cell expansion. The growth factor most usually employed for chondrogenic development belongs to the TGF- super family. These are bone morphogenic proteins (BMP-2, 4, 6, 7), cartilage-derived morphogenic proteins (CDMP-1, 2), and transforming growth factor beta-1 (TGF-1). Reverse dedifferentiation, chondrogenic differentiation, and the production of extra cellular matrix, a crucial component of chondral tissue, are all processes that are especially aided by these factors. The chondrogenic differentiation factors FGF-2 and FGF-18 appear to have distinct effects on MSCs and chondrocytes. The FGF family does have a considerable effect on MSCs, although its benefits for chondrocyte metabolism might not be as great. Another growth factor linked to the development of cartilage is insulin-like growth factor (IGF-1), which promotes the actions of TGF and BMP-7 and enhances anabolic pathways while suppressing catabolism in cells. IGF-1 has been found to work in concert with TGF and BMP-7 to enhance chondrogenic differentiation in MSCs[32]. It has been found that chondrocyte number and proteoglycan production decrease with reduced IGF-1[33]. Another growth factor that promotes chondrocyte proliferation and proteoglycan production is platelet derived growth factor (PGDF). Moreover, it has been shown that PGDF reduces IL-1 levels, which are known to cause chondral deterioration[34]. Growth factors that both stimulate and inhibit chondrocyte metabolism are concentrated in these injections because they are made up of a variety of growth factor types with distinct functional activities[35]. The ease of obtaining autologous growth factors makes these treatments advantageous, but their main drawback is the lack of standardization and accurate measurement of factor concentrations[36].

IX. ADVANCING TECHNIQUES

More contemporary cell culture approaches have been researched with the goal of altering the cell microenvironment to promote cell differentiation and provide better quality

regenerative synthesis[37]. Techniques Improved cell proliferation has been achieved using methods for building three-dimensional MSC cultures and scaffolds[38]. It has also been researched to use varying hydrostatic pressures, mechanical stress, and low oxygen tensions as culture methods. These variations can be added to the cell culture by utilizing bioreactors made to resemble physiological in vivo environments. It has been proven that applying cyclically increased hydrostatic pressures to MSC cultures increases the production of cartilage matrix even in the absence of chondrogenic growth stimuli[39]. Several studies have discovered that cultures that were mechanically loaded with dynamic, shear, or compression stresses exhibited increased chondrogenesis. More chondrogenic differentiation and matrix production are accomplished by giving the chondrocytes additional mechanical stimulation that mimics joint response stresses. According to these results, it is most likely that for increased chondrogenesis, cells require both growth hormones and mechanical pressures to induce more natural cellular responses.

REFERENCES

[1] Gorbachova, T., Melenevsky, Y., Cohen, M., and Cerniglia, B. W. (2018). Osteochondral lesions of the knee: differentiating the most common entities at MRI. Radiographics 38, 1478–1495. doi: 10.1148/rg.2018180044

[2] Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: a review of 31,516 knee arthroscopies. Arthroscopy. 1997 Aug;13(4):456-60. doi: 10.1016/s0749-8063(97)90124-9. PMID: 9276052.

[3] Madry, H., van Dijk, C. N., and Mueller-Gerbl, M. (2010). The basic science of the subchondral bone. Knee Surg. Sport Traumatol. Arthrosc. 18, 419–433. doi: 10.1007/s00167-010-1054-z

[4] Mente, P. L., and Lewis, J. L. (1994). Elastic modulus of calcified cartilage is an order of magnitude less than that of subchondral bone. J. Orthop. Res. 12, 637–647. doi: 10.1002/jor.1100120506

[5] Stewart, H. L., and Kawcak, C. E. (2018). The importance of subchondral bone in the pathophysiology of osteoarthritis. Front. Vet. Sci. 5:178. doi: 10.3389/fvets.2018.00178

[6] Bauer, M., & Jackson, R. W. (1988). Chondral lesions of the femoral condyles: a system of arthroscopic classification. Arthroscopy: The Journal of Arthroscopic & Related Surgery, 4(2), 97-102.

[7] Bohndorf K. Osteochondritis [osteochondrosis] dissecans a review and new MRI classification. Eur Radiol. 1998;8:103–112.

[8] Lyons, T. J., McClure, S. F., Stoddart, R. W., and McClure, J. (2006). The normal human chondro-osseous junctional region: evidence for contact of uncalcified cartilage with subchondral bone and marrow spaces. BMC Musculoskelet. Disord. 7:52. doi: 10.1186/1471-2474-7-52

[9] Sophia Fox, A. J., Bedi, A., and Rodeo, S. A. (2009). The basic science of articular cartilage: structure, composition, and function. Sports Health 1, 461–468. doi: 10.1177/1941738109350438

[10] Hayes, W. C., and Bodine, A. J. (1978). Flow-independent viscoelastic properties of articular cartilage matrix. J. Biomech. 11, 407–419. doi: 10.1016/0021-9290(78)90075-1

[11] Woo, S. L.-Y., Mow, V. C., Lai, W. M., Skalak, R., and Chien, S. (1987). "Biomechanical properties of articular cartilage," in Handbook of Bioengineering, eds R. Skalak and S. Chien (New York, NY: McGraw-Hill Book Co), 4.1–4.44.

[12] Tisano, B., Ellis, H. B., Wyatt, C., & Wilson, P. L. (2022). Osteochondral Allograft for Unsalvageable Osteochondritis Dissecans in the Skeletally Immature Knee. Orthopaedic Journal of Sports Medicine, 10(2), 23259671211072515.

[13] Herring, M. J., Knudsen, M. L., and Macalena, J. A. (2019). Open reduction, bone grafting, and internal fixation of osteochondritis dissecans lesion of the knee. JBJS Essent. Surg. Tech. 9:e23. doi: 10.2106/jbjs.st.18.00035

[14] Millington, K. L., Shah, J. P., Dahm, D. L., Levy, B. A., and Stuart, M. J. (2010). Bioabsorbable fixation of unstable osteochondritis dissecans lesions. Am. J. Sports Med. 38, 2065–2070. doi: 10.1177/0363546510371369

[15] Vogel, L. A., Fitzsimmons, K. P., and Lee Pace, J. (2020). Osteochondral fracture fixation with fragment preserving suture technique. Arthrosc. Tech. 9, e761–e767. doi: 10.1016/j.eats.2020.02.018

[16] Matsusue, Y., Yamamuro, T., and Hama, H. (1993). Arthroscopic multiple osteochondral transplantation to the chondral defect in the knee associated with anterior cruciate ligament disruption. Arthroscopy 9, 318–321. doi: 10.1016/S0749-8063(05)80428-1

[17] Richter, D. L., Tanksley, J. A., and Miller, M. D. (2016). Osteochondral autograft transplantation: a review of the surgical technique and outcomes. Sports Med. Arthrosc. 24, 74–78. doi: 10.1097/JSA.0000000000000099

[18] Solheim, E., Hegna, J., Strand, T., Harlem, T., and Inderhaug, E. (2018). Randomized study of long-term (15-17 years) outcome after microfracture versus mosaicplasty in knee articular cartilage defects. Am. J. Sports Med. 46, 826–831. doi: 10.1177/0363546517745281

[19] Stevenson, S., Shaffer, J. W., and Goldberg, V. M. (1996). The humoral response to vascular and nonvascular allografts of bone. Clin. Orthop. Relat.Res. 323, 86–95. doi: 10.1097/00003086-199605000-00011

[20] Nielsen, E. S., McCauley, J. C., Pulido, P. A., and Bugbee, W. D. (2017). Return to sport and recreational activity after osteochondral allograft transplantation in the knee. Am. J. Sports Med. 45, 1608–1614. doi: 10.1177/0363546517694857

[21] Sherman, S. L., Garrity, J., Bauer, K., Cook, J., Stannard, J., and Bugbee, W. (2014). Fresh osteochondral allograft transplantation for the knee: current concepts. J. Am. Acad. Orthop. Surg. 22, 121–133. doi: 10.5435/JAAOS-22-02-121

[22] Lo, B., and Parham, L. (2009). Ethical issues in stem cell research. Endocr. Rev. 30, 204–213. doi: 10.1210/er.2008-0031

[23] Mafi, R. (2011). Sources of adult mesenchymal stem cells applicable for musculoskeletal applications - a systematic review of the literature. Open Orthop. J. 5, (Suppl. 2), 242–248. doi: 10.2174/1874325001105010242

[24] Berebichez-Fridman, R., Gómez-García, R., Granados-Montiel, J., Berebichez-Fastlicht, E., Olivos-Meza, A., Granados, J., et al. (2017). The holy grail of orthopedic surgery: mesenchymal stem cells - their current uses and potential applications. Stem Cells Int. 2017:2638305. doi: 10.1155/2017/2638305

[25] Sakaguchi, Y., Sekiya, I., Yagishita, K., and Muneta, T. (2005). Comparison of human stem cells derived from various mesenchymal tissues: Superiority of synovium as a cell source. Arthritis Rheum. 52, 2521–2529. doi: 10.1002/art.21212

[26] de Mara, C. S., Sartori, A. R., Duarte, A. S., Andrade, A. L. L., Pedro, M. A. C., and Coimbra, I. B. (2011). Periosteum as a source of mesenchymal stem cells: The effects of TGF-β3 on chondrogenesis. Clinics 66, 487–492. doi: 10.1590/S1807-59322011000300022

[27] Jackson, W. M., Nesti, L. J., and Tuan, R. S. (2010). Potential therapeutic applications of muscle-derived mesenchymal stem and progenitor cells. Expert Opin. Biol. Ther. 10, 505–517. doi: 10.1517/14712591003610606

[28] Yu, J., Vodyanik, M. A., Smuga-Otto, K., Antosiewicz-Bourget, J., Frane, J. L., Tian, S., et al. (2007). Induced pluripotent stem cell lines derived from human somatic cells. Science 318, 1917–1920. doi: 10.1126/science.1151526

[29] Chijimatsu, R., Ikeya, M., Yasui, Y., Ikeda, Y., Ebina, K., Moriguchi, Y., et al. (2017). Characterization of mesenchymal stem cell-like cells derived from human iPSCs via neural crest development and their application for osteochondral repair. Stem Cells Int. 2017:1960965. doi: 10.1155/2017/1960965

[30] Sakaguchi, Y., Sekiya, I., Yagishita, K., and Muneta, T. (2005). Comparison of human stem cells derived from various mesenchymal tissues: Superiority of synovium as a cell source. Arthritis Rheum. 52, 2521–2529. doi: 10.1002/art.21212

[31] Sohni, A., and Verfaillie, C. M. (2013). Mesenchymal stem cells migration homing and tracking. Stem Cells Int. 2013:130763. doi: 10.1155/2013/130763

[32] Zhou, Q., Li, B., Zhao, J., Pan, W., Xu, J., and Chen, S. (2016). IGF-I induces adipose derived mesenchymal cell chondrogenic differentiation in vitro and enhances chondrogenesis in vivo. Vitr. Cell. Dev. Biol. Anim. 52, 356–364. doi: 10.1007/s11626-015-9969-9

[33] Wei, F. Y., Lee, J. K., Wei, L., Qu, F., and Zhang, J. Z. (2017). Correlation of insulin-like growth factor 1 and osteoarthritic cartilage degradation: a spontaneous osteoarthritis in guinea-pig. Eur. Rev. Med. Pharmacol. Sci. 21, 4493–4500.

[34] Schmidt, M. B., Chen, E. H., and Lynch, S. E. (2006). A review of the effects of insulin-like growth factor and platelet derived growth factor on in vivo cartilage healing and repair. Osteoarthr. Cartil. 14, 403–412. doi: 10.1016/j.joca.2005.10.011

[35] Rutgers, M., Saris, D. B. F., Dhert, W. J. A., and Creemers, L. B. (2010). Cytokine profile of autologous conditioned serum for treatment of osteoarthritis, in vitro effects on cartilage metabolism and intra-articular levels after injection. Arthritis Res. Ther. 12:R114. doi: 10.1186/ar3050

[36] chahla, J., Cinque, M. E., Piuzzi, N. S., Mannava, S., Geeslin, A. G., Murray, I. R., et al. (2017). A call for standardization in platelet-rich plasma preparation protocols and composition reporting. J. Bone Jt. Surg. 99, 1769–1779. doi: 10.2106/jbjs.16.01374

[37] Vats, A., Bielby, R. C., Tolley, N., Dickinson, S. C., Boccaccini, A. R., Hollander, A. P., et al. (2006). Chondrogenic differentiation of human embryonic stem cells: the effect of the micro-environment. Tissue Eng. 12, 1687–1697. doi: 10.1089/ten.2006.12.1687

[38] Estes, B. T., and Guilak, F. (2011). Three-dimensional culture systems to induce chondrogenesis of adipose-derived stem cells. Methods Mol. Biol. 702, 201–217. doi: 10.1007/978-1-61737-960-4_15

[39] Puetzer, J., Williams, J., Gillies, A., Bernacki, S., and Loboa, E. G. (2013). The effects of cyclic hydrostatic pressure on chondrogenesis and viability of human adipose-and bone marrow-derived mesenchymal stem cells in three-dimensional agarose constructs. Tissue Eng. Part A 19, 299–306. doi: 10.1089/ten.tea.2012.0015

