Biology of Cartilage Regeneration

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Articular Cartilage Structure and Composition

The function of the articular cartilage is to provide for smooth, pain-free gliding of the joints during skeletal motion. Articular cartilage is composed of a large extracellular matrix, synthesized by the chondrocytes, including type II collagen and proteoglycan aggregates. Collagen fibers give cartilage its form and tensile strength, and water constitutes 75–80 % of cartilage weight, functioning largely in compression. Chondrocytes are responsible for maintaining the matrix, which involves degradation by proteinases, aggrecanase, and oxygen free radicals, which may be generated by the chondrocyte [1]. The structure of articular cartilage can be divided into zones—superficial, middle, and deep—each of which imparts mechanical properties contributing to the articular surface [1] (Fig. 65.1). In the superficial zone, the chondrocytes are flattened and collagen fibrils are aligned parallel to the surface. The primary function of this layer is to resist shear forces. Cells in this zone synthesize a molecule called "superficial zone protein" providing the almost frictionless articulation by the articular cartilage. The middle zone is composed of obliquely oriented collagen fibers and primarily resists compression forces. In the deep zone, fibers are oriented perpendicular to the subchondral plate, resisting both compression and shear forces. Calcified cartilage in the deep layer provides a buffer with intermediate mechanical properties between the more superficial uncalcified cartilage and the underlying subchondral bone. The avascular nature of articular cartilage makes it dependent on diffusion through the matrix for nutrition. Diffusion of nutrients from subchondral bone vessels and synovial tissue play a critical role in maintaining normal adult cartilage homeostasis and function [2].

Healing Capacity of the Cartilage

Both partial and full-thickness lesions have limited capacity for repair. In animal models, after the creation of osteochondral defects, generally good reconstitution of the articular cartilage is observed as early as four weeks. However, early traces of degeneration are seen after 12 weeks and continue to progress with time [3]. Not only is the immediate area of the defect affected but the articular cartilage adjacent to defect also degenerates, suggesting a "zone of influence" which may explain the progression of a focal chondral defect to more diffuse degeneration [4]. Differences in the potential for cartilage repair separate acute injuries of articular cartilage into three general types: (1) loss of matrix macromolecules or disruption of the macromolecular framework without visible tissue disruption, (2) mechanical disruption of articular cartilage alone, and (3) mechanical disruption of articular cartilage and subchondral bone:

1. *Loss of matrix macromolecules*: This may alter chondrocyte function or even damage the chondrocytes. Chondrocytes can sense changes in matrix composition and synthesize new molecules, which allow the cells to repair damage to the macromolecular framework. Available evidence indicates that repair of the matrix in response to loss of proteoglycans may require many weeks and possibly months. If the cells fail to repair significant matrix macromolecular abnormalities, or if the loss of matrix molecules progresses, the tissue will deteriorate with time. The threshold for irreversible injury and progressive loss of articular cartilage is unknown [5, 6].

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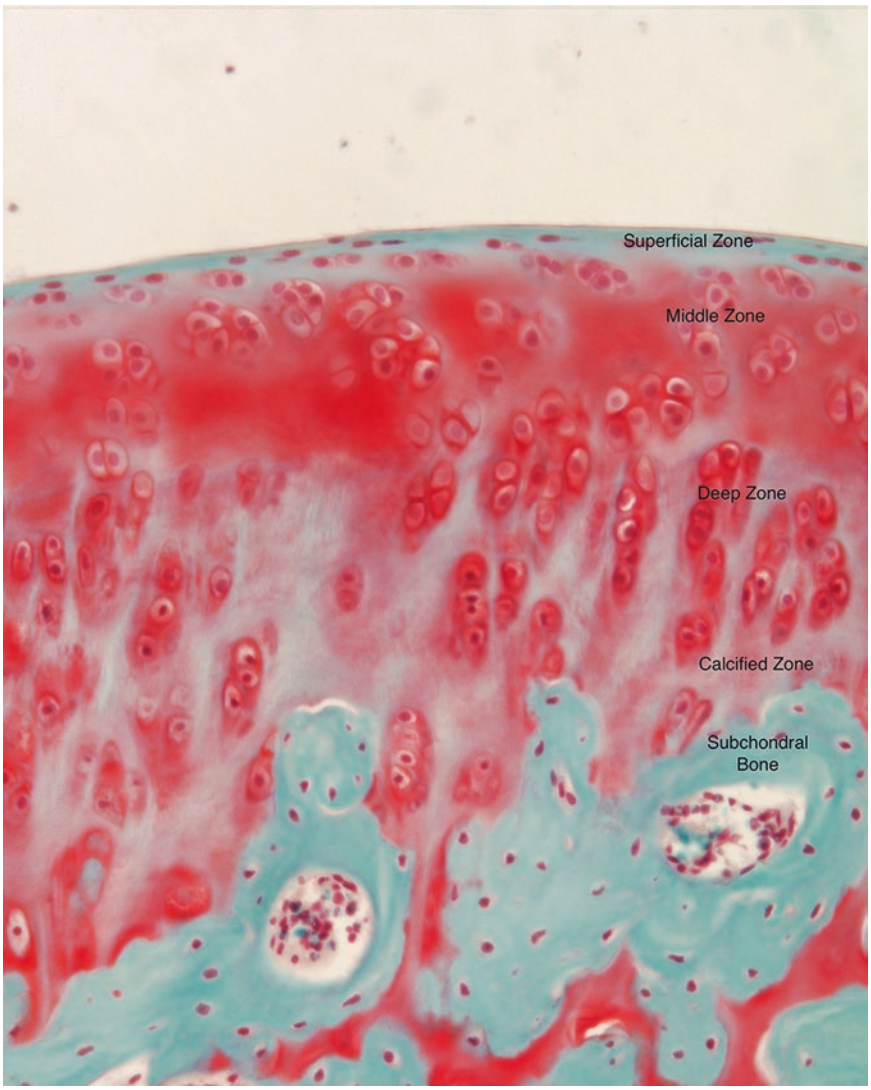

Fig. 65.1 Microscopic anatomy of articular cartilage. Safranin O staining. Note the superficial, middle, and deep zone with the decreased content of aggrecan

2. *Mechanical disruption of articular cartilage alone*: When injury is limited to the cartilage tissue, the local response depends entirely on the chondrocytes. Undifferentiated mesenchymal cells cannot migrate from blood vessels to the site of injury. The chondrocytes near the injury site respond to tissue injury by proliferating and increasing synthesis of matrix macromolecules, however, the newly synthesized matrix and proliferating chondrocytes are unable to fill the tissue defect, and soon after injury, the increased proliferation and synthetic activity ceases [7].
3. *Injuries affecting Cartilage and Subchondral Bone*: When a joint injury extends into the subchondral bone, hemorrhage occurs with fibrin clot formation and activation of an inflammatory response. In animal experiments, repair tissue fills about two-thirds of the total volume of the chondral portion but most of the filling is performed in the bone portion of the osteochondral defect [8]. The tissue in the chondral and bone portions of the defect differs significantly in composition. The chondral repair tissue does not contain bone or blood vessels and has a significantly higher proportion of hyaline-like cartilage or fibrocartilage. Whereas, the repair tissue within the subchondral bone is highly vascular and endochondral bone formation is normally evident [3]. With time the cartilage repair tissue occasionally persists unchanged or progressively remodels. Most of the time, the chondral repair tissue begins to show depletion of matrix proteoglycans, with progressive degeneration through fibrillation and fragmentation.

Many factors that prevent cartilage from healing have been suggested, including joint environment, age, changes in epigenetics, apoptosis, and biochemical constitution of the repair tissue [9–11].

Several factors are felt to contribute to the failure of attempts to perform surgical repair of cartilage lesions, including abnormalities in the biochemical constitution of the repaired tissue, the quality of its physicochemical binding

to the adjacent cartilage, and the altered stiffness of the repaired subchondral bone [12]. The reparative tissue is weaker, with higher water and lower proteoglycan content compared to normal-appearing cartilage [13].

The potential for cartilage healing is also strongly influenced by the age of the patient, with repair usually occurring in the growing child but not in the adult [12, 14]. Cartilage matrix turnover and remodeling is much more rapid in a child as part of the growth process. In adults, although synthesis increases in damaged cartilage, these newly synthesized molecules are degraded [15, 16]. Stimulation of matrix synthesis alone is not sufficient to ensure the success of a reparative process, as the newly synthesized molecules must be protected from proteolysis to ensure their incorporation and retention in the newly repaired matrix [17].

Changes in the joint environment after cartilage injury have also been implicated in cartilage degeneration. After cartilage trauma, there is an increased expression of metalloproteinases (MMP), (ADAMTS-5), and caspases (3–9), which promote chondrocyte apoptosis [11, 18–21]. There are also inflammatory mediators, such as interleukin-1 beta, which have degradative effects on cartilage matrix.

Ongoing research to identify the factors that prevent cartilage from healing will allow development of interventions that may enhance cartilage repair or even prevent cartilage from degeneration.

Current Techniques for Cartilage Regeneration in the Hip

The options for surgical treatment of articular cartilage lesions can be divided into palliative, reparative, and restorative procedures. Palliative procedures, including debridement and lavage, are done primarily for symptomatic relief and have little potential for cartilage regeneration. Reparative techniques attempt to restore the integrity of the native subchondral interface and preserve the overlying articular cartilage [22]. These include drilling and ORIF, normally used for OCD lesions in the talus and knee [23]. Finally, restorative procedures attempt to replace damaged cartilage with hyaline or hyaline-like tissue [24]. When performing the treatment of cartilage lesions, the surgeon must consider the "next step" option if initial surgical management fails. The treatment algorithm proceeds from the least destructive and invasive methodologies, to preserve the ability to use additional options should initial treatment fail. Although there has not been any published data yet on how to proceed with cartilage lesions in the hip, one should assume that the treatment algorithm should be similar to other joints [25]. Thus the algorithm for treatment of hip lesions is likely to include consideration of the anatomic location of the lesion (acetabulum versus femoral head), and its size (small vs big), and depth (superficial versus deep). Concomitant pathology such as FAI (femoro-acetabular impingement) (Cam-Pincer lesion), labrum tears, or hip dysplasia should always be considered and treated simultaneously.

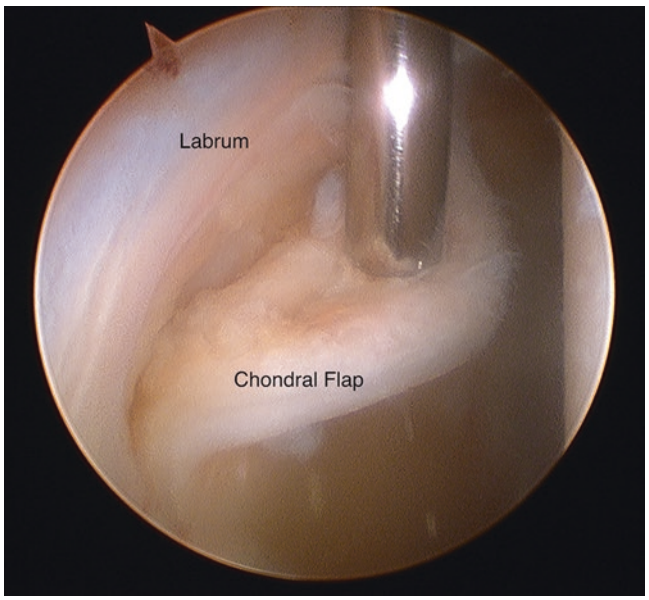

Fig. 65.2 Note typical flap chondral lesion that is observed in patients with a CAM lesion. Location is normally in the acetabulum and in the anterosuperior area

Table 65.1 Classification of cartilage damage

Description	Criteria
Normal	Macroscopically sound cartilage
Malacia	Roughening of surface, fibrillation
Debonding	Loss of fixation to the subchondral bone, macroscopically sound cartilage; carpet phenomenon
Cleavage	Loss of fixation to the subchondral bone; frayed edges, thinning of cartilage, flap
Defect	Full-thickness defect

Intraoperative classification for chondral lesions in the hip as proposed by Beck et al. [30]

Cartilage lesions have a typical pattern in patients with CAM lesions [26, 27] and are most commonly located in the anterosuperior area of the acetabulum [28]. The commonly accepted mechanism of injury is exposure of the labrochondral junction to repetitive compression and shear that occurs when the CAM lesion slides into the anterosuperior acetabulum during flexion and internal rotation. This causes the labrum to be stretched and displaced peripherally while the cartilage is compressed and pushed centrally resulting in separation between the labrum and cartilage, and, in many cases, a typical flap chondral lesion (Fig. 65.2). These chondral defects may cause pain, and, if left untreated, will likely progress to more generalized degeneration [27, 29]. Classification of cartilage damage in the acetabulum has been proposed by Beck et al. [30] (Table 65.1).

Cartilage restorative procedures such as marrow stimulation or microfracture, fresh osteochondral allografts, osteochondral autografts (OATS), and autologous chondrocyte implantation (ACI) have been extensively described in different joints including knees, shoulders, and ankles [25] (Figs. 65.3 and 65.4). However, there is currently very little published data on the outcome of cartilage repair in the hip.

Microfracture is one of most widely cartilage therapy used to treat cartilage lesions in the hip. This technique is normally indicated for small chondral lesions, no bigger than 10 mm in any dimension. These lesions are normally seen in patients with CAM lesions in the anterosuperior area of the acetabulum (Figs. 65.5 and 65.6).

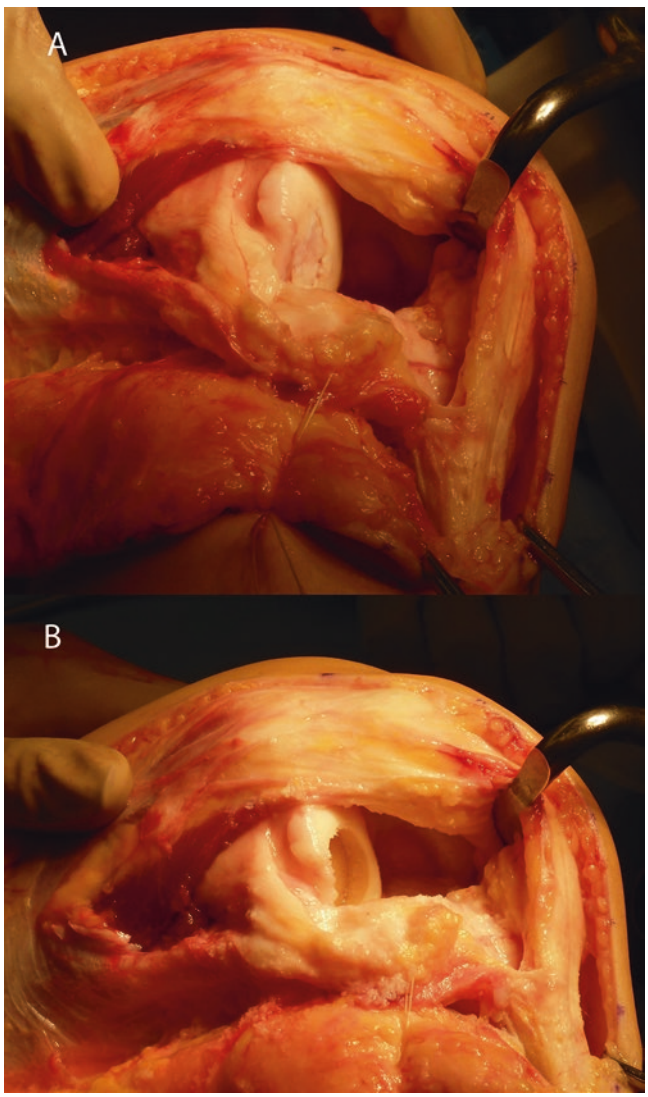

Fig. 65.3 (**a**) A chondral defect is evident in the lateral femoral condyle. This patient underwent a combined distal femoral osteotomy, osteochondral allograft, and meniscus allograft transplantation. An arthrotomy with a proximal extension for exposure of the distal femur was performed. (**b**) The defect was prepared using the recipient harvester instrument

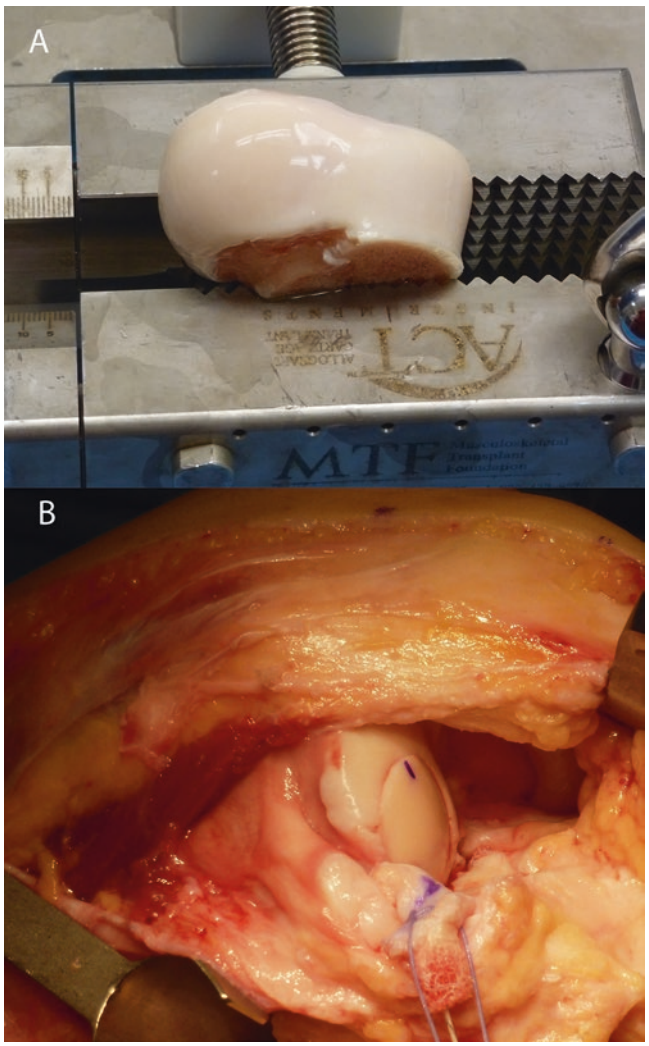

Fig. 65.4 (**a**) Donor condyle secured on a device that holds the graft while the donor segment is harvested. (**b**) The osteochondral plug was placed into the recipient defect. The 12 o clock position was marked on the allograft, representing the most superior point of the defect

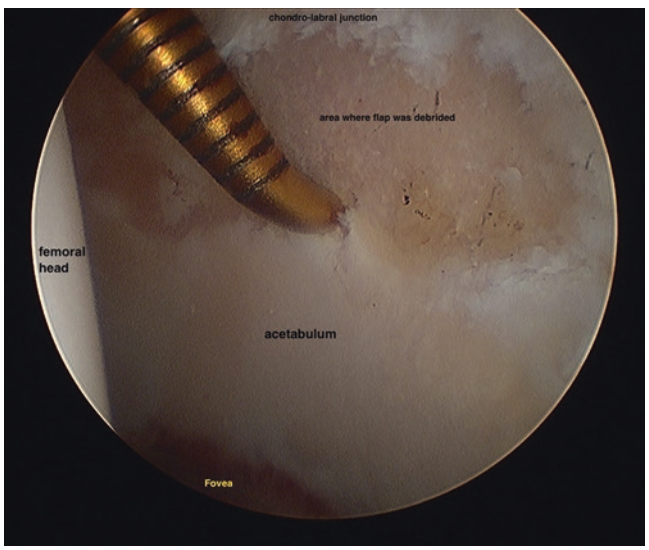

Fig. 65.5 Note the chondral lesion, already debrided and prepared for microfracture. Using an awl, microfracture was performed

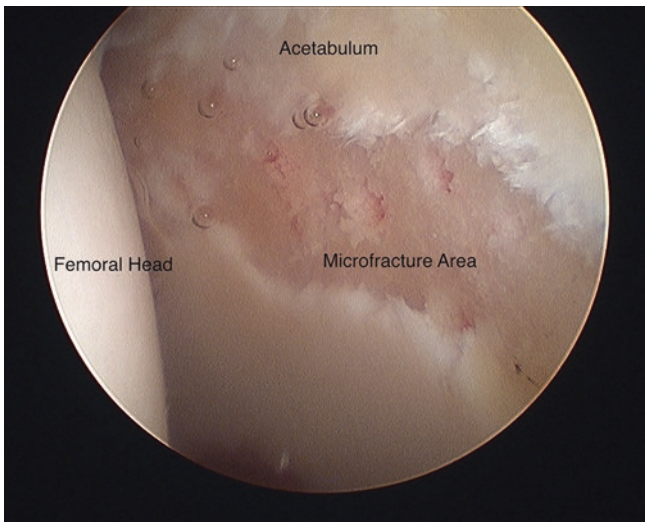

Fig. 65.6 Microfracture was performed. The microfracture holes are evident in the chondral lesion

Clinical results have been encouraging [31–33]. Karthikeyan et al. recently published the results observed with microfracture for acetabular chondral defects in patients with FAI [33]. All patients had a second look arthroscopy at an average 17 months post microfracture. Repair tissue was assessed as described by Blevins et al. [34]. Fill rate of the chondral lesions were reported in 93 % of the patients. Clinically, the NHS (nonarthritic hip score) improved from 55 to 78 after microfracture. Histologically, the tissue appeared to be fibrocartilage. Collagen type I and II was present in most samples. Philippon et al. [32] reported 95–100 % fill in eight of the nine patients who had second-look hip arthroscopic surgery after microfracture for acetabular cartilage lesions. They demonstrated an average fill of 91 % at an average follow-up of 20 months. No clinical evaluation was performed in this study.

Mosaicplasty or OATS should be considered for larger cartilage lesions or those with involvement of the subchondral bone. These lesions normally occur over the femoral surfaces of patients who sustain traumatic hip dislocations or patients with AVN (avascular necrosis). Mosaicplasty has shown excellent results in the knee [35, 36]. However, in the hip, literature is lacking with only isolated case reports. In all of these reports, short-term outcomes are encouraging, suggesting patients may return to normal activity with no progression of cartilage degeneration. Gagala et al. recently published clinical and radiological results for the treatment of AVN (avascular necrosis) of the femoral head using OATS in 20 patients [37]. At 18 months post operative, they reported clinical improvement (HHS from 42 to 87) with only one patient requiring a THR. At the moment, this technique can only be performed with an open dislocation of the hip, which adds morbidity. Future studies of a larger series of patients will further evaluate the effectiveness of this technique for traumatic osteochondral injury of the femoral head.

Autologous chondrocyte implantation (ACI) has been widely used in the last 15 years for the repair of cartilage defects [38]. It has been shown to be successful in the treatment of full-thickness defects in the knee and ankle, especially in young and active patients. There is only on case report of ACI for AVN of the hip [25, 39, 40]. Similar to OATS, this procedure was performed with an open dislocation.

More advanced techniques such as use of juvenile allograft cartilage (De Novo NT ®), CAIS (cartilage autograft implantation system), MACI (matrix autologous chondrocyte implantation), second- and third-generation ACI and characterized chondrocyte implantation (CCI) are becoming popular in the treatment for chondral lesions in the knee and may play a future role in cartilage restoration in the hip [34–36, 41]. Clinical results of MACI technique in the hip have been reported. The technique proposed is performed arthroscopically. At 5 years post-operative, patients improved clinically with no reported failures or adverse events [42, 43]. Continued development of an arthroscopic surgical technique for the treatment of chondral lesions in the hip with cell therapies will improve future applicability [44].

Future Directions

Future directions in cartilage regeneration are focusing on growth factors, stem cells, and new biomaterials, together with improvement in early diagnosis using MRI imaging and novel biomarkers [45]. Various growth factors continue to be investigated as a treatment for early joint pain or osteoarthritis and for cartilage regeneration, and they were recently reviewed [46]. Combinations of anabolic growth factors such as OP-1 and IGF-1 appear to be the most promising growth factor approach due to a synergistic effect [47]. The use of stem cells to regenerate articular cartilage remains a topic of active investigation. Novel biomaterials that are able to recruit endogenous stem cells to the site of injury rather than implanting exogenous cells is also a promising area of investigation. Ongoing studies are aimed at understanding why and how stem cells "home" to sites of injury. Progenitor stem cells have been identified in normal human articular cartilage. These studies have suggested that cartilage progenitor cells may be a superior cell source to mesenchymal stem cells. Additional studies are required to understand how to recruit these resident cartilage progenitor cells to the site of damage [48–50].

The therapeutic use of autologous platelet-rich plasma (PRP) constitutes a relatively new biotechnology that may play a role in the stimulation and acceleration of cartilage healing [51–53]. Chondrocytes and MSCs (mesenchymal stem cells) exposed to PRP both have increased cell proliferation

and cartilage extracellular matrix synthesis of proteoglycans and collagen type II compared with controls [54].

There is very little data on clinical results of the treatment of early OA of the hip with PRP. The optimal PRP formulation, timing, and number of injections are still controversial. Different PRP preparations are available, which makes it even more difficult to compare results. Battaglia et al. recently reported the outcomes of injection of PRP for OA of the hip. All patients had significantly improved clinical symptoms at short-term follow-up. No major complications or adverse events occurred at the time of injection or in the follow-up period [55].

Magnetic resonance imaging (MRI) of cartilage continues to be the optimal modality for detailed cartilage imaging. In addition to the traditional morphologic assessment, more advanced quantitative cartilage imaging techniques, such as T1ρ, T2 mapping, and dGEMRIC are increasingly being used to noninvasively assess the biochemistry of the cartilage repair and to diagnose preclinical disease. The concept is that if signatures of cartilage damage could be detected early, prior to development of morphologic abnormalities, then early interventional therapies could be applied to prevent rather than to slow or diminish the degenerative process.

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