

Microfracture

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The technique of microfracture (MFX) was first performed 40 years ago and served for many years as the main procedure for repairing cartilage defects. There is a need to improve microfractures because the regenerated cartilage differs from the original histological aspect; it is less hyaline and more fibrocartilaginous. In addition, and more importantly, the benefits do not persist and the long-term results are unsatisfactory.

Keywords: microfracture ; hyaluronic ; platelet-rich plasma ; adipose derived mesenchymal stem cells ; chitosan-based scaffold

1. Introduction

Today, management strategies are oriented toward symptom control, so conservative treatment should serve as a first-line therapy. Different guidelines have recommended various non-operative treatments, such as exercise, weight control, acetaminophen, transcutaneous electrical nerve stimulation, oral NSAIDs, intra-articular injections, and other methods. The surgical procedure of replacing the joint is reserved for severely affected joints [1].

As a degenerative pathology, OA leads to irreparable cartilage lesions. Although joint replacement is an effective surgical intervention, in order to prevent the development of osteoarticular disease and avoid this major surgical procedure, other less invasive methods should be attempted, such as microfracture (MFX), alone or in combination with intra-articular injection of adipose-derived stem cells (ADSCs), bone marrow aspirate concentrate (BMAC), platelet-rich plasma (PRP), hyaluronic acid (HA), or cell-free scaffolds [2].

Cartilage lesions are a common issue and are present in more than 60% of knees on arthroscopy. About 5% are seen in younger patients under 40 years old. The management of cartilage lesions represents one of the most challenging problems for the orthopedic community. None of the existing techniques can fully restore the cartilage to its hyaline aspect [3].

The technique of microfracture was first performed 40 years ago and served for many years as a main procedure for repairing cartilage defects. The goal of this intervention is to provide the patient with both surgical and functional benefits. Throughout the years, the technique has constantly been improved by various researchers. There is a need to perfect MFX because the regenerated cartilage differs from the original histological aspect; it is less hyaline and more fibrocartilaginous. Moreover, the MFX procedure uses an awl to penetrate the bone, which leads to subchondral bone alterations such as cysts and a lower subchondral bone health score. These findings may affect clinical outcomes and may be responsible for the biological and mechanical impairment of the fibrocartilage repair tissue in the medium term and, possibly, the long term. Adjunctive treatments include platelet-rich plasma, hyaluronic acid, adipose-derived mesenchymal stem cells, and chitosan-based bioscaffolds (**Table 1**) [4][5].

Table 1. The main adjuvant treatments with MFX.

Adjuvant MFX	Brief Definition
Mesenchymal stem cells	Characterized by the capacity to go through self-renewal and multi-lineage differentiation and create fully differentiated cells [6]
Platelet-rich plasma	Autologous concentration of human thrombocytes in a small quantity of plasma [7]
Hyaluronic acid	Natively occurring glycosaminoglycan with elasticity and viscosity properties that acts as a lubricating and shock absorbing liquid in joints [8]
Chitosan-based scaffolds	Chitosan, the main constituent, is obtained from de-acetylation of chitin, the structural component of crustacean shells; it has reduced toxicity and good biocompatibility, adhesivity, and biodegradability [9]

Adjuvant MFX	Brief Definition
Collagen-based scaffolds	Collagen, the main constituent, is the most abundant protein in the extracellular matrix of many hard and soft tissues in the human body; the most important is type I collagen, which provides structural support to resident cells in both types of tissue ^[40]

2. Microfracture Alone

The procedure starts with the creation of three portals around the knee; for the inflow cannula, the working instruments, and the arthroscope. First, an elaborate evaluation of the knee is carried out, including the suprapatellar pouch, patellofemoral joint, medial and lateral gutters, notch, and medial and lateral compartments. After visualization of the cartilage defect, the uncovered bone is debrided of any remaining cartilage tags by using a resector, and the intact cartilage around the defect is surgically prepared in order to form a pool where a clot can form. The calcified layer of cartilage that remains is delicately detached with a shaver. Caution must be taken not to harm the subchondral bone. Next, an arthroscopic awl is utilized to create a series of holes (microfractures) in the uncovered subchondral bone. The holes are about 3 to 4 mm apart and with a depth of 4 mm. This is the optimal distance that avoids the possible confluence of one hole into another. Typically, the microfractures are started from the periphery, moving to the center of the cartilage defect. After that, blood and droplets of fat from the holes can be observed ^{[4][11][12]}.

The penetrated subchondral bone plate leads to the formation of a clot in the defect. This clot comprises pluripotent mesenchymal stem cells derived from the marrow, which will fabricate a fibrocartilage repair with varying quantities of type II collagen ^[13].

Although this is an inexpensive, easy, and popular technique, various studies have reported a series of limitations. The most important are that the benefits are not persistent, and the long-term results are unsatisfactory. Goyal et al. conducted a systematic review of 15 studies, and the overall results showed that microfracture has good results at short-term follow-up, but beyond 5 years postoperatively, failure can be expected, regardless of the size of the lesion. Oussedik et al. also performed a systematic review of bone marrow stimulation techniques, including MFX. They also found good early results, but noted that due to the abnormal new cartilage, unsatisfactory results can be expected in the long run, especially in larger defects ^{[14][15]}.

3. Microfracture Plus Scaffolds and Stem Cells

Over the last few years, mesenchymal stem cell-based treatments for the regeneration of cartilage defects have received significant recognition for various reasons. The capacity of MSCs to turn into connective tissue, such as hyaline cartilage, and the ease of obtaining them from diverse tissues (bone marrow, adipose tissue, trabecular bone, etc.) make them easy targets regarding the harvesting of cells. Among them, ADSCs are easy to obtain for clinical use, with increased isolation yields, and are not altered by the patient's sex, age group, or physiological status. The available studies performed on animals suggest that intra-articular injection of human ADSCs can facilitate regeneration of articular cartilage ^{[3][16][17]}.

The process includes isolating ADSCs one day before the MFX. The stromal vascular fraction and MSCs are isolated from adipose fragments obtained from the patient. Cells are cultured in T-25 flasks at a final concentration, in order to assess the quantity of mesenchymal-like progenitors in the stromal vascular fraction ^[18].

After the arthroscopic bone marrow stimulation procedure of MFX described above, a fibrin scaffold is introduced in two separate syringes. One syringe contains lyophilized human plasma fibrinogen in 1 mL of aprotinin solution and the other has thrombin in a calcium chloride solution. The glue is intended to immediately form a gel when the two solutions are combined. The cell suspension (stromal vascular fraction containing MSCs) is loaded into the thrombin solution in a 1:1 ratio. Then, the cell–thrombin suspension is added to the fibrinogen solution (1:1) using a syringe support system, and they are implanted together into each source on the cartilage lesion surface. The most suitable option for implantation of this cell–thrombin–fibrinogen suspension is through arthroscopic guidance after the arthroscopic liquid is drawn ^[16].

The available data are in favor of MFX + ADSC therapy. A systematic review conducted by Arshi et al. in 2017 includes 18 articles that compare various MFX + techniques with MFX alone. Out of the 18, two studies dealt with ADSCs as an injectable augmentation to MFX. The outcomes showed statistically significant improvement on the postoperative International Knee Documentation Committee Subjective Knee Form (IKDC) and Knee injury and Osteoarthritis Outcome Score (KOOS) two years after the procedure. After that, only two important studies have been published on this topic. Qiao et al. divided the subjects into three categories: treatment with arthroscopic MFX and intra-articular injection of normal saline (M group), MFX + HA (MS group), and MFX + HA + ADSCs (MSR group). Patients in the MS and MSR

groups showed a meaningful response to therapy, based on clinical evaluation of Western Ontario and McMaster Universities Arthritis Index (WOMAC) and 36-Item Short Form Survey (SF-36) scores. Regarding the quantitative evaluation of defect size and cartilage volume by MRI and arthroscopy, the two groups also showed significant improvements. During the first 9 months after treatment, the discrepancies between groups were non-significant. However, after 12 months, clinical improvements were significantly greater in the MSR group than the M and MS groups, on most scales. The M group managed to maintain clinical improvement for 9 months; after that, the benefits of microfracture were progressively lost. This finding is in agreement with published studies that also claim that after 1 year the clinical benefits of MFX alone begin to diminish. In the MS and MSR groups, clinical benefits also appeared to diminish after 1 year, but the patient outcomes were still slightly improved at 24-month follow-up compared to baseline. However, these findings are hardly sufficient to recommend ADSCs as an augmentation to MFX, due to the need for an additional surgery ^{[21][19]}.

Another noteworthy study, conducted by Hashimoto et al., compared MFX alone ($n = 4$) with MFX + ADSCs ($n = 7$). They found no significant differences in preoperative and postoperative IKDC and KOOS scores between the two groups. Despite that, after 48 weeks, the MFX + group had a higher KOOS quality of life (QOL) score compared with the MFX alone group. Moreover, the T2 value (mapping of magnetic resonance images) showed no significant differences, but the mean magnetic resonance observation of cartilage repair tissue (MOCART) score was significantly higher in the MFX + group ^[20].

Bone marrow aspirate concentrate is another biologic adjunct. Intra-articular delivery of bone marrow concentrate was shown to improve MFX outcomes in full-thickness cartilage defects in a horse model. BMAC concentrations are higher in the iliac crest compared to tibial or femoral bone marrow blood. This finding has led to the development of BMAC and a protective scaffold that can treat chondral lesions when combined with MFX. This is a single-stage procedure, where a large number of multipotent cells are able to differentiate toward the chondral lineage and improve the defect filling and the rate of hyaline-like repair ^{[21][22]}.

Murphy et al. divided 101 patients into an MFX group ($n = 52$) and MFX + BMAC group ($n = 49$). They compared complications, revision rates, and visual analogue pain scores. They stated that MFX + BMAC appeared to be a safe and effective treatment option for chondral injuries of the talus, decreasing the revision rates without any complications at the donor site ^[23].

A retrospective study conducted by Jin et al. evaluated MFX alone (group I, 43 cases) and MFX + BMAC (group II, 48 cases). Of these, 64 patients underwent a second-look arthroscopic assessment. Clinical outcomes were similar between the two groups, but the cartilage repair assessment (CRA) grade was significantly higher with BMAC augmentation after two years. Therefore, MFX + BMAC resulted in better cartilage regeneration, although studies with longer follow-ups might be needed to confirm these findings ^[24].

4. Microfracture Plus Platelet-Rich Plasma

Although microfracture is a safe and encouraging treatment for musculoskeletal diseases, evidence of its success has varied greatly and is very indication-specific. After setting the MFX holes, the arthroscopic liquid is cleared from the joint in order to create a dry environment for the application of the PRP mixture. The cubital veins can be used to collect 30 to 45 mL of whole blood into a 50 mL syringe that contains sodium citrate. The blood is anticoagulated and centrifuged at 1500 rpm for 10 min. After a second spin of 3000 rpm for 5 min, about 5 mL of PRP is obtained for each person. The PRP is infiltrated into the knee treated by MFX. This procedure can be repeated regularly, and patients follow a standard rehabilitation protocol ^{[25][26][27]}.

PRP can be used to augment MFX due to the ability of platelets to liberate a series of growth factors that have an important role in building higher-quality cartilage. Arshi et al. included the effects of MFX + PRP in their systematic review. They obtained statistically significant improvements in postoperative IDKC and KOOS scores at 2 years. The newest meta-analysis dealing with the evaluation of PRP as an adjuvant for microfracture is by Boffa et al. (2020). They analyzed seven studies that met the inclusion criteria and suggested that PRP can improve the outcomes of MFX in knees and ankles at short-term follow-up. However, these ameliorations did not reach minimal clinically important differences (MCIDs), and thus they were not clinically perceivable by patients ^{[19][28]}.

Recently, Yang et al. conducted a study on 79 patients, divided into a control group of 39 patients treated with MFX + PRP and an observation group of 40 treated by MFX alone. Parameters such as baseline data, pain level, knee range of motion, knee symptoms, motor function, knee function, and complications were evaluated. Significantly statistical results

were obtained for IDKC scores ($p < 0.05$) and for Tenger and Lysholm scores ($p < 0.05$). The rate of complications was also better for the group treated with PRP as an adjuvant (10%, compared to 28% in the control group). Follow-up was done at 1, 2, and 3 months after surgery [29].

5. Microfracture Plus Cell-Free Injectable Scaffolds

There are three basic elements in tissue engineering: cells, biodegradable scaffolds, and growth factors, which together provide a new method for the repair of articular cartilage. Scaffolds can provide a 3D structure for cartilage cells and favor cell adhesion and proliferation. They also mediate the signals and interactions between cells. The available literature offers various cell-free injectable scaffolds for treating cartilage lesions, such as HA-based, collagen-based, and chitosan-based [30].

Hyaluronic acid is a lubricant designed to reduce the pain and inflammation of articular surfaces and completes the endogenous joint fluid. Intra-articular injections are utilized for cartilage lesions and joint degeneration. HA has a high-molecular-weight glycosaminoglycan component, which is the reason for its viscoelastic attributes. Moreover, in order to provide joint lubrication and shock absorption, HA represents the main way for proteoglycans of the extracellular matrix to create a hydrated pathway through which cells can migrate [31][32].

HA as a scaffolding material depends largely on its bulk surface. The parameters that are used to describe the network structure of hydrogels include the molecular weight of the polymer chains, the corresponding mesh size, and the effective network density. HA-based scaffolds can bind to proteins and cells through cell surface receptors, such as CD44, RHAMM, and ICAM-1. HA scaffolds can bind to chondrocytes via CD44. Multiple biological processes mediated by these scaffolds are important for the wound healing process. This, coupled with the capacity to offer an open, hydrated structure for the passage of nutrients, makes them candidates for tissue regeneration and repair techniques [33][34].

Research has revealed that scaffolds made from dehydrated cartilage can stimulate adult stem cells to differentiate down a chondrogenic pathway, producing cells that show morphologic, molecular, and biochemical characteristics that resemble those of articular cartilage cells. The scaffolding allows for hyaline-like cartilage to regenerate within the defect, which enables better structural support for the defect and improved longevity of the repair [35].

Brusalis et al. conducted a study where they evaluated the short-term outcomes of microfracture augmented with a micronized allograft cartilage matrix (BioCartilage) and PRP for symptomatic focal femoral condyle or trochlea cartilage defects. MRI investigations were performed 1 year after the intervention. At 2 years, the outcomes were evaluated through patient-reported outcome measures (PROMs) and the rates of return-to-work and return-to-sport. They concluded that focal chondral lesions treated with the adjuvant therapy were associated with significant improvements in PROMs 2 years postoperatively [36].

A multicenter randomized controlled trial performed by Lee et al. compared 46 patients divided into two equal groups, one treated with MFX alone and one with MFX plus atelocollagen augmentation. After 2 years of follow-up, the quality of the regenerated cartilage was superior after the augmentation technique. Although all clinical outcomes evaluated were superior in patients who underwent arthroscopic MFX with atelocollagen augmentation, the differences were not statistically significant [37].

In another study conducted by Kim et al., 28 patients were divided into two groups; patients who underwent high tibial osteotomy (HTO) with MFX alone or HTO plus MFX and collagen augmentation. One year after treatment, a second-look arthroscopy was performed in order to obtain a biopsy of the repaired cartilage. The quality of the repair after MFX with collagen augmentation was superior compared with MFX alone. In terms of the clinical scores after one year, no differences were observed [38].

Despite all of the above studies regarding collagen-based scaffolds showing great potential, further research is needed to evaluate longer-term outcomes and durability.

6. Current Insights and Future Directions

Up-to-date evidence regarding the enhancing agents presented in this review highlights that they can serve as routine adjuncts to MFX in the future. The goal is to produce a hyaline cartilage, and MFX alone has been shown to be prone to failure in this respect, inducing less adequate fibrocartilaginous tissue. Adjuvant therapies are constantly being developed and advanced in terms of biocompatibility, chemical structure, combination strategies, and methods of administration, in

order to provide higher-quality tissue. Although they are relatively new approaches, the literature offers other cartilage tissue regeneration techniques that are worth mentioning [39].

One such therapy, which is gaining popularity, is the intra-articular injection of various types of blood-derived products. Kuten-Pella et al., using a 3D osteoarthritic chondrocyte pellet model, evaluated the regenerative potential of two types of PRP, one prepared with EDTA and citrate and an alternative blood product, hyperacute serum (hypACT). They obtained the best results for hypACT and stated that the possible molecular mechanisms of blood-derived products should be investigated in order to obtain the best results [40].

Moreover, due to the significant progress made in genetic and biochemical research in recent years, the molecular basis of cartilage lesions has become better understood. Our understanding of their complex genetic background has led to the development of new targeted therapies. The technology of delivering therapeutic genes to the site of injury and integrating tissue engineering with viral gene vectors is a novel and emerging approach to cartilage renewal. However, despite the encouraging preclinical results, the concept requires more clinical trials in order to become a therapeutic option for cartilage treatment [41].

Another approach worth mentioning consists of a modified gelatin hydrogel that absorbs proteoglycans secreted by chondrocytes near the cartilage tissue in situ and quickly forms an adequate chondrocyte survival microenvironment. Wang et al. evaluated this therapeutic method, and the in vivo and in vitro results showed that the hydrogels were effective and expressed efficient biocompatibility, while promoting the tissue repair of cartilage defects [42].

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