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Chapter

Fat Tissue's Graft in Osteoarthritis Treatment: Indications, Preparations, and Results

Edoardo De Fenu, Berardino Di Paola, Marco Ruggiero, Bruno Carlesimo, Andrea Conversi and Ezio Adriani

Abstract

Osteoarthritis (OA) represents one of the most common causes of joint pain and disability with related changes in bone morphology. In last years, this pathology is steadily increasing due to the continuous increase in the average life expectancy and the rate of active population. In recent years, there have been many conservative treatments for symptomatic gonarthrosis in order to reduce pain and delay or avoid the implantation of a knee prosthesis. The most studied and used was infiltrating treatment. Our group has been paying attention to regenerative medicine for many years, focusing on the characteristics of adipose tissue and the presence of multipotent mesenchymal cells, particularly in the vascular stromal area. Mesenchymal stem cells (MSCs) of adipose tissue can commit toward the chondrogenic, osteogenic, adipogenic, myogenic, and neurogenic lineages. Our group has continued the studies in this field by submitting this to treatment patients with grade II–III arthrosis according to the scale of Kellgren-Lawrence or patients with IV degree of such scale inoperable for internal reasons. To date, with a 4-year follow-up, our results are satisfactory in terms of pain reduction, improvement in joint function, and recovery of daily and sports activities.

Keywords: osteoarthritis, fat tissue, joint, adipose stem cells, conservative treatment

1. Introduction

Osteoarthritis is a common degenerative joint cartilage disorder associated with hypertrophic bone changes and loss of joint cartilage integrity [1]. It causes pain, stiffness, and reduction of the associated function, consequently, disability with relative difficulty for the patient in carrying out the normal daily activities [2]. Risk factors are represented by genetic factors, female sex, post-traumatic conditions, age, obesity, etc. [3–6]. Treatment is therefore aimed at reducing symptoms, improving quality of life, and preventing its progression. Treatment options can be classified into:

- Conservative treatment, such as lifestyle education, pain therapy and physiotherapy, and infiltrative therapy.

- Surgical treatment, traditionally represented by arthroplasty and osteotomy and in some cases by arthroshaving [2].

Several national and international OA management guidelines recommend that patients should be first introduced into pathways that provide conservative treatment options and then directed to surgical treatment only when the conservative treatment does not allow the desired therapeutic achievement [7–10].

2. Epidemiology and causes

It represents the most common joint disease in the world, even if the frequencies vary from country to country: it affects more than 40 million individuals only in the United States and about 4 million in Italy, thus representing the main cause of disability at a national level. Therefore, OA is responsible for direct and indirect medical costs for society: clinical visits by primary care physicians or specialists, drugs, and surgical interventions represent direct costs; comorbidity and time lost from work due to the effects of disability are the examples of indirect costs. This clinical condition is more evident among the elderly, who may lose their independence and then need assistance during their daily activities, thus increasing the economic burden [11–13]. The lifetime risk of developing symptomatic osteoarthritis of the hip is 18.5% for men and 28.6% for women. For symptomatic knee OA, it is around 45%. Therefore, the risk of being subjected to a total hip or knee prosthesis at the age of 50 results to be high, with values of 7.1–11.6% for the hip and 8.1–10.8% for the knee [14, 15].

OA has a multifactorial etiology, and it is a disease that affects not only the quality of all synovial joint structures but also the function and quality of surrounding tissues and the pathway of nociceptive signaling. The causes that lead to the onset of osteoarthritis are largely unknown. On the other hand, it is believed that in most cases, many factors that alter the joint balance are involved. Schematically, the joint balance can be maintained if a normal load is exerted on a normal cartilage. Therefore, all factors capable of modifying this balance, acting either on the load or modifying the characteristics of cartilage, can be considered risk factors for osteoarthritis. In most cases, there is a combination between the genetic predisposition of the individual and the influence of environmental factors, especially those that act on the load, such as mechanical stress, obesity, malformations, trauma, and microtrauma. The precocity of the onset and the type of evolution may then depend on the number of factors involved, on their size and on the duration of their action. The OA can be divided into primary and secondary forms. The primary form, or idiopathic, manifests itself in intact joints without any triggering factor. Aging plays a fundamental role in this form of OA: the joint wear causes damage to the cartilage and, associated with an abnormal repair mechanism, the disease manifests itself. In the secondary form, OA is caused by a predisposing factor. In general, any violation of the integrity of the chondrocyte matrix has the potential to cause OA. However, some considerations aside highlight age as a risk factor. Although we all know that the frequency of arthrosis increases with age, arthritis is currently considered not to be a disease of aging. In fact, not all the elderly has this disease. It is therefore probable that the genetic tendency that an individual has in the predisposition to contract sooner or later some diseases, including arthritis, can be accentuated and accelerated by the risk factors. Obviously, among the elderly, the duration of exposure to these risk factors is higher, so the consequences are more evident.

Some risk factors are not changeable, such as age and genetic predisposition, while others, such as mechanical ones, overweight, etc., are considered modifiable and therefore, a rarely feasible consideration for other rheumatic diseases [16, 17].

Attention must also be given to another attachment of the joints overlapping the OA for clinical and disability: osteonecrosis. Osteonecrosis is estimated to be the cause of 10% of all total hip arthroplasty performed in the United States.

However, differentiation between these conditions can be difficult, particularly at the beginning of the pathological process [18, 19].

It is a disease characterized by the interruption of the normal supply of bone blood resulting in "death" bone. At this point, the healing response may be inadequate and then the joint surface collapses with the subsequent degenerative arthritis [18].

Osteonecrosis is more common in patients under the age of 40 and has no sexual preference. Among the risk factors acquired for osteonecrosis, alcohol abuse, smoking, and trauma are more common in men, while rheumatic diseases, such as systemic lupus erythematosus, are more commonly found in women. Therefore, the predilection of sex in osteonecrosis is highly influenced by the associated risk factors [20].

OA develops with the combination of biochemical, cellular, and mechanical processes [21].

OA is associated with biochemical events mediated by cytokines, proteolytic enzymes, and other proinflammatory substances responsible for osteolysis, subchondral bone sclerosis, osteophytosis, articular erosion of the cartilage, and thickening of the synovial membrane [22, 23].

Following the break of the cartilaginous matrix, due to proteolysis, the cartilage weakens and becomes subject to fibrillation and erosion, resulting in the release of proteoglycans and collagen fragments in the synovial fluid. This process induces an inflammatory response in the synovium, which causes further degradation of the cartilage. When the cartilage weakens, it begins to thin out, causing a reduction in joint space. Cartilage damage also causes the appearance of periarticular osteophytes. The exact mechanism of pain generation in OA is not well understood, but is probably related to an interaction of different mechanisms [21, 24].

From a purely biochemical point of view, OA is the result of an imbalance between the peptides that promote the synthesis of components of the ECM (extracellular matrix) of the articular cartilage and those that induce the remodeling of these components. [25–31].

The result of these catabolic cascades is the persistence of the synovitis, with initial cartilage damage and induction of remodeling of the subchondral bone [32, 33]. The pathogenesis of OA is therefore composed of a network of overlapping complex molecular mechanisms, which entail damage to the articular tissue. These mechanisms depend on the equilibrium of expression of the catabolic and anabolic articular molecules.

3. Therapy

The goals of therapy in OA can be defined as "short-term," represented by pain control, stiffness control, and reduction of inflammation and "medium-long term," represented by the arrest or slowing of progression, by deformity prevention, and restoration of function.

For the pursuit of these objectives, many strategies can be used, both pharmacological and nonpharmacological, which often need to be coordinated with each other to be really effective. In fact, in addition to the introduction of new drug therapies, the importance of general measures, such as patient education to the

knowledge of the disease and the consequent implementation of some measures such as weight loss and gymnastics or the use of unloading orthoses is recommended [10, 34, 35].

For conservative treatment, today we have several strategies available that, as mentioned, where possible, must be evaluated and taken into account in relation to the clinical condition of the patient.

An increasingly important role in the conservative treatment of OA is represented by the infiltrative therapy that in recent years has proposed a wider range of solutions: from intra-articular anti-inflammatory therapy as a palliative treatment to an infiltrative solution that can restore joint homeostasis or that can possibly activate a regenerative process into the joint.

Intra-articular corticosteroid injections may be indicated after failing NSAIDs and acetaminophen, but some researchers suggest only using them once every 3 months for a maximum of 2 years due to negative potential side effects [36].

The mechanism underlying the anti-inflammatory efficacy of corticosteroid is multifactorial, but generally involves blocking antigen opsonization, leukocytic cell adhesion, and cytokine diapedesis within the capillary endothelium. Corticosteroids also attenuate the effects of IL-1, decrease leukotriene and prostaglandin release, and inhibit metalloproteases and immunoglobulin synthesis [37].

The duration of action of intra-articular corticosteroid injections remains controversial, with various studies quoting anywhere between 1 and 24 weeks. There is consensus that steroids provide relief to patients for approximately 1 week after injection.

Adverse effects of corticosteroid injections do exist; however, Handler and Wright first described radiographic evidence of destruction of the knee joint and cartilage after several corticosteroid injections [38]. The incidence of joint infection following corticosteroid administration is rare, but may be as high as one in 3000 patients, with an associated mortality rate of approximately 11%. Additional known complications include pain, skin atrophy, tendinopathy, and systemic hyperglycemia [39].

The use of this procedure results in an inconclusive recommendation strength [10].

4. Hyaluronic acid injections

HA plays a fundamental role in maintaining elasticity and viscosity of the synovial fluid and integrity of the connective tissues such as joints [40, 41]. Several studies have shown that HA is a chondroprotector: it synthesizes proteoglycan and glycosaminoglycan, and it has anti-inflammatory, mechanical, subchondral, and analgesic actions [40].

5. Platelet-rich plasma

Platelet-rich plasma (PRP) is the most investigated biological treatments [42–44] due to the capacity to reduce inflammation and consequently a reduction of pain [45–47]. PRP exerts its biological effect with neoangiogenesis and migration of macrophages and mesenchymal cells and regulates cell differentiation and the activity of different cell lines, promoting tissue regeneration. PRP is controversial for the treatment of OA, because there is insufficient evidence to recommend the use of it [48–50].

Despite the growing interest in this biological approach for cartilage regeneration, the knowledge on this topic is still preliminary [51].

6. Biological use of fat tissue

The promise of mesenchymal stem cells (MSCs) to give birth to a new era of medicine was strong, thanks to the ability of these cells to do self-renewal and multipotent *in vitro* differentiation into mesodermal cell subtypes. To be honest, recent studies have demonstrated that a good portion of the thrilling *in vivo* clinical results is due to the trophic, paracrine, and immunomodulatory activities of MSCs instead of their differentiation ability [52]. Differently from drug concept where the effect is dependent from concentration, MSCs are self- and site-regulated and they release a multitude of bioactive factors in variable concentration in response to the local messages of the microenviroment. The main trophic activity exerted by MSCs is the release of growth factors and other chemokines to induce the homing and proliferation of cellular progenitors and to promote angiogenesis. These factors are transforming growth factor beta (TGF-β), hepatocyte growth factor (HGF), endothelial growth factor (EGF), fibroblast growth factor 2 (FGF-2), and insulin-like growth factor 1 (IGF-1)—all of these are proteins able to accelerate cellular growth and division of progenitors [53]. Moreover, IGF-1, EGF, and the vascular endothelial growth factor (VEGF) are able to recruit endothelial cells and promote new vascularization [54].

MSCs can derive from many tissue sources, and among these, the more manageable for clinical practice is bone marrow and adipose tissue. Even if the MSCs from bone marrow (BM-MSCs) were discovered first and have more clinical experience, there is higher interest on adipose tissue—not only for the ease and low morbidity of harvest but also because it has a higher MSCs frequency. In a bone marrow aspirate, there are 6×10^6/ml nucleated cells and, among these, only 0.001–0.01% are MSCs; on the other hand, a lipoaspirate contains $0.5–2.0 \times 10^6$/g nucleated cells where the MSCs frequency ranges from 1 to 10% based on the donor site. Since the adipose tissue has a total of $0.5 \times 10^4–2 \times 10^5$/g of MSCs, it means that there is a 500-fold higher concentration of MSCs in comparison with bone marrow [55]. Moreover, it has been demonstrated that the proliferation and differentiation properties of stem cells from adipose tissue (ADSCs) are less impaired by age in comparison with BM-MSCs [56].

ADSCs can be exploited with three different methods. The first, the only option where we can properly name them as true ADSCs, is the cell culture and optional cell expansion *in vitro*. By selecting the cells that are able to stick to the plastic, it is possible to obtain cell that expresses mesenchymal markers (CD105+, CD73+, CD90+, CD45−, CD34−, CD11b−, CD14−, CD79a−, and HLA-DR−) able to differentiate into the three mesodermal lineages (bone, cartilage, and fat). This option has serious limitation in the clinical practice due to regulatory issues because it can only be performed into good manufacturing practice facilities that manipulate these cells like an experimental drug (it is named advanced cellular therapy). Notably, concentrated BM-MSCs outperform cultured cells since they are more practical and efficient and less harmful and expensive [52]. The second method is enzymatic digestion of adipose tissue that gives in the hands of operators a heterogeneous cell population that contains, beside MSCs, endothelial cells, leucocytes, and preadipocytes. This final product of enzymatic digestion is named stromal vascular-fraction (SVF). Finally, autologous ADSCs can be exploited through the processing and fragmentation of adipose tissue (FAT, *fragmented adipose tissue*). While the SVF is a heterogeneous cell population where each cell is separated from the others and the efficacy is dose-dependent, the FAT is a proper minimally manipulated tissue that entrust more on cell quality instead of cell quantity. The FAT is composed of tissue cluster of variable diameter where the SVF cells are embedded and attached to an undisrupted tissue architecture made of vasculature and extracellular matrix sustained by a scaffold made of adipocytes. This natural scaffold protects cells from anoikis (death cause by the lack of cellular adherence) and other harmful stress.

The MSCs embedded into these clusters have high vitality and can still differentiate into the three mesodermal lineages as a proof of their multipotency. To prove that quality is superior to quantity, it has been demonstrated in an animal model of critical limb ischemia that an injection of 500 μl of FAT (which contain 2×10^4 ADSC) restores limb perfusion better than a single injection of 1×10^6 isolated ADSC [57].

During the First World War, the fat was used to heal soldier wounds and its application was very heterogeneous until 1990 where Sidney Coleman defined precise guidelines. The evolution of surgical techniques associated the volumizing effect of lipofilling to the regenerative properties of natural adipose tissue, favoring the processing, the reduction, and the purification of the tissue to raise the survival of grafts and magnify the regenerative potential of MSCs. Also reducing the volume of grafts and the diameter of injection needles had helped the hosting tissue to decrease stress and trauma, thus provoking less inflammation and ameliorating again graft survival [58]. Adipose tissue is now used with lipofilling techniques in hard-to-heal wounds and in all cases characterized by mortified tissue (burn, compression, and radiation) linking the regenerative potential also to an esthetic effect. Wound healing professionals use lipofilling to treat ulcers resistant to classical therapies and advanced dressing and also for the treatment of critical limb ischemia and diabetic patients [59]. In orthopedics, intra-articular lipofilling has become a fashionable and innovative strategy to fight osteoarthritis, thanks to the ability of this tissue product to reequilibrate the articular homeostasis and to reduce the inflammation of the synovial membrane [60]. The integrity of the extracellular matrix can also exploit the shock absorber function of adipose tissue reducing the stress between cartilage surfaces. The paracrine effect of MSCs can also promote cartilage repair when mechanical conditions of the articulation are stable. The anti-adhesive properties of adipose tissue were exploited in the surgery of tendons and nerves to limit the formation of fibrotic and scarring tissue, thus also limiting the relapse incidence. Finally, adipose tissue was also studied in pain management for the intradiscal infiltration for the treatment of low back pain associated to black disc.

7. Lipofilling

The technique of liposculture is originally created for esthetic purposes. Autologous fat transfer has recently become an increasingly popular surgical procedure: harvesting, refinement/processing, and transfer of subcutaneous tissue to provide relatively pure and intact parcels of fat are paramount for successful lipofilling. Usually, we use local anesthesia with sedation or epidural anesthesia. Rarely, we use general anesthesia.

- Incisions with a n°11 blade are made in the donor site. When possible, incisions are placed in wrinkle lines, folds, or fatty areas (abdomen flank, thigh, and knee).

Instruments for lipofilling cause minimal trauma to fatty tissue during placement.

- Cannulas vary in shape (curved or no-curved) and length (7–12 cm).

Liposuction: special blunt-tip, maximum diameter 3 mm, with small holes near the tip

  - Coleman I is used near a blood vessels or nerve. This cannula is capped on the tip with a lip that extends 180° over the distal aperture.

- Coleman II is used in other circumstances. This cannula is not completely capped and has a lip that extends over the distal aperture about 130–150°.

- Coleman III is used for the scars or fibrous tissue treatments. This cannula is flat on the end to allow for dissection of the tissue.

- Coleman V is a dissector used for scar's treatment.

Transplantation: small blunt-tip

- Infiltration cannula is a blunt 17G cannula with one or two distal aperture proximal to the tip: no fatty tissue should be infiltrated during the advancement of the cannula; fatty tissue is left in the pathway of the retreating blunt cannula (this method permits stable and regulated placement with minimal irregularities or clumps of tissue).

8. Surgical technique

8.1 Harvesting of adipose tissue from a suitable donor site

Many different techniques have been proposed for harvesting of adipose tissue: the fundamental aim is minimizing adipocyte damage and increasing the survival of adipose tissue. Incisions with a n°11 blade are made in the donor site, when possible in wrinkle lines, folds, or fatty areas (abdomen, flank, thigh, and knee).

There are many different natural fat deposits: it is important an accurate preoperative examination of the patient.

The abdomen is the most common site of fat harvesting; it is also common in the trochanteric region (saddlebags) and in the medial/internal part of the thighs and knees.

The main techniques for fat harvesting are vacuum suction, syringe suction, or surgical excision.

8.1.1 DRY technique

Other surgeons advocate a "dry" fat harvesting: cell viability has been similar to "wet" fat harvesting nut, and this technique may lead to a greater requirement for analgesic.

8.1.2 WET technique

In 1993, Klein proposed a new method called tumescent technique in which a fluid solution (Klein's solution) was injected into the donor site improving the safety of large-volume liposuction (it eliminated the need for general anesthesia and reduced surgical hemorrhage).

Another technique is the "Berlin autologous lipotransplantation", which involves the use of a water-jet system to harvest the fat tissue and collect it in a closed container: minimal bruising and postoperative pain, faster harvesting time, and greater sterility.

In the course of fat harvesting, a blunt cannula is inserted through an incision into fatty tissue engorged with tumescent fluid (Klein's solution)

- Negative pressure liposuction is faster than 10 ml syringe aspiration (low pressure) and is an effective method for aspiration of large amounts of fat, but it causes massive destruction of adipocytes, greatly reducing the survival of fat graft.

- Conventional liposuction with high negative pressure may cause disruption of 90% of adipocytes structures.

Cannula size may also impact the viability of harvested adipocytes. Performing biopsy and lipoaspiration with large-bore cannulas could reduce the risk of cellular rupture by preserving native tissue structure.

So the size of cannula must be large enough to preserve adipocytes and stromal cells and their anatomical relationship without limiting diffusion of nutrients.

Coleman described a technique for fat harvest that minimized trauma to the adipocytes.

He used 3-mm incisions (n°11 blade), a 3-mm blunt edge, 2 hole harvesting cannulas (3 mm) connected to a 10-ml Luer-Lock syringe. The cannula is pushed through the harvest site (abdomen, flank, thigh, knee, or other sites with excess adipose tissue) as the surgeon uses digital manipulation to create a gentle negative pressure.

A combination of lower negative pressure and the curetting action of the cannula through the tissues allows parcels of fat to move into the syringe. At the end, the syringe is disconnected from the cannula and replaced with a plug that seals the Luer-Lock end of the syringe.

8.2 Processing

The most commonly used methods to process fat tissue are centrifugation, sedimentation, washing, and filtration. Comparative studies investigating the effects of fat processing with different techniques have showed no significant differences in fat retention.

The goal of fat processing is:

To eliminate contaminants that can cause inflammation at the recipient site, which can be detrimental for the fat graft. These elements include cellular debris, free oil, and other nonviable components of the lipoaspirate such as hematogenous cells.

- Blood must be extracted in order to improve degradation of the transplanted fat.

- Since the debris will be absorbed after a few hours, its injection could be confused with volume correction.

- Moreover, many authors report an improvement in graft viability by maximizing the number of ADSC in the graft material.

8.3 Ensuring graft viability

Centrifugation is the most widely used technique for postharvest fat processing and has previously been considered the criterion standard. Coleman's technique consisted in centrifugation (3000 rpm for 3 minutes) to separate the different components as follows:

- Upper level: least dense and consists primarily of oil.

- Middle: primarily fatty tissue.

- Lowest: blood, water, and aqueous elements.

The supernatant fat and the lower aqueous layers are discarded, leaving concentrated viable fat cells.

That is an optimal method to obtain the highest concentration of stem cells and increased angiogenic grow factors (FGF and VEGF). It separates adipocytes from blood cells and enzymes (lipids, proteases, and lipases). Sedimentation allows obtaining a large number of vital intact adipocytes [61].

Washing methods has the goal of removing superfluous tumescent fluid and all elements that can be detrimental for the fat graft.

- Lipocell technique is a new procedure that allows eliminating blood, oil, cellular debris, or other nonviable components and obtaining a pure lipoaspirate. This technique preserves a large number of mesenchymal stem cells and a large number of adipocytes.

Filtration allows elimination of contaminants by maintaining viable adipocytes and a lot of ADSC, thus obtaining a viable graft material for large volume fat transfers.

- Pure graft filtration is a new technology that uses a closed-membrane filtration system for preparation and isolation of stromal vascular fraction and its mechanism is known to work by principles similar to a dialysis unit.

8.4 Implantation/fat injection

Principles of fat reimplantation are found on optimal recipient site vascularity to increas fat survival.

Graft can survive up to 48 hours by tissue fluid absorption.

Neovascularization progresses 1 mm/day; therefore, a deposit diameter greater than 2 mm should be avoided to prevent central necrosis. With a skin incision like a diameter of the cannula, the graft is put at the level of the anatomical region involved. Cannulas with small gauge will reduce tissue trauma, bleeding, and hematoma.

Through multiple access sites, multiple tunnels are created on insertion, but fat is injected only during withdrawal of the cannula.

In our experience, mainly concentrated on the knee involves the constant association of a diagnostic and surgical arthroscopy; in fact, in the majority of cases, there are meniscal lesions (flap type) or unstable chondral lesions which, if left untreated, could lead to failure of the grafting procedure alone.

9. Complications

All steps in surgical technique (harvesting, processing, and transplantation) are important. Complications are few, rare, and minimal. Viability of fat cells is crucial. The chances of survival are higher if the fat graft is less manipulated and reinjected as fast as possible.

- Donor site complications related to lipoaspirate technique: bruising, swelling, hematoma, pain, paresthesia, infection, pathologic scarring, contour irregularities, cellulitis, and damage to the underlying structures.

- Failure of fat graft in recipient sites could cause fat necrosis, oil cysts, calcifications, reabsorption of fat, and intravascular injection with fat embolism.

Early identification of local sepsis.

10. Conclusion

In conclusion, there are several treatments for knee OA including nonpharmacological and pharmacological treatments.

Among the nonpharmacological ones, patient education and self-management strategies, advising weight loss and strengthening programs are included.

Regarding the pharmacological treatment, the NSAIDs can be used in the short-term therapy but their effect is limited in time.

Another employed strategy to manage knee OA is represented by joint injections of corticosteroids, hyaluronic acid, PRP, and even stem cells [47].

The reason for using ASCs in orthopedics is derived from tissue engineering studies that enhance their ability to differentiate into osteoblastic or chondrocyte using appropriate culture media and bioengineered structures that can accommodate cells as a biological scaffold.

The studies of Hattori and colleagues showed an osteogenic differentiation (by electron microscope, with histological evaluation and by the capacity of osteocalcin secretion) analogous to BMSC using a beta-tricalciophosphate scaffold [62, 63].

Always Hattori and colleagues in 2008 proposed new strategies for the in vitro expansion of ASCs. In most cases, the expansion was obtained with fetal bovine serum (FBS) which, in subsequent clinical applications, could have caused infections or immunological reactions caused by the proteins present in the FBS [64].

For this reason, Hattori and colleagues have demonstrated, with studies on the mouse, that it is possible to obtain the expansion of the ASC with the same differentiation potentials, using a small amount of autologous serum containing type I, FGF-2 collagen and thus opening the way to possible therapeutic applications.

Promising is the application in the treatment of cartilaginous lesions. In 2007, Masuoka and colleagues used a three-dimensional honeycomb scaffold of atelocollagene (ACHMS scaffold) with ASCs for cartilaginous lesions in rabbit's knees; as a control group, they used the only ACHMS-scaffold or nothing [65]. Twelve weeks later, histological analyzes have highlighted that only in cases where ASC + ACHMS-scaffold had been used, there was hyaline cartilage with high expression of type II collagen. It should be also noted that the ASCs, as mentioned above, have the ability to release factors of tissue growth and/or regeneration and cytokines. These substances play an important role in chemotaxis, in promoting tissue regeneration, cell differentiation, and neoangiogenesis.

Regenerative medicine opens the way for a new therapeutic frontier, as it now allows an improvement in symptoms and in the functionality of the joints. On the other hand, further studies are needed, major follow-ups, targeted clinical trials, and finally the possibility of a second look to evaluate and validate the real regenerative capacity of this treatment.

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