

R E V I E W

Current concepts in treatment of early knee osteoarthritis and osteochondral lesions; the role of biological augmentations

C. Dall'Oca, M. Cengarle, A. Costanzo, N. Giannini, A. Vacchiano, B. Magnan

Clinica Ortopedica, Azienda Ospedaliero Universitaria Integrata, Verona

Summary. Early knee osteoarthritis and chondral lesions are a common cause of disability in younger patients. Surgical options, such as microfractures, ACI and OAT, provide good, but not fully satisfying, outcomes. Recent advance in biological knowledge introduced two different methodological approaches of delivering growth factors and stem cells into the articular environment. Platelet-Rich Plasma and Mesenchymal Stem Cells are supposed to change the way to approach early knee osteoarthritis and chondral lesions, though their indications and limits are yet to be determined. (www.actabiomedica.it)

Key words: knee OA, osteochondral lesion, MSCs, ASCs, PRP, stem cells

Introduction

The knee is the most common site of osteoarthritis (OA). The PRO.V.A. study estimated a prevalence of 20,4% of knee osteoarthritis in people aged 65 years or older in Italy (1). The 2010 EULAR recommendations for diagnosis of knee OA (KOA) (2) and recent research (3) suggest to consider it as a whole joint disease, characterized by cartilage loss, subchondral bone remodeling, osteophyte formation and involvement of soft tissues such as synovial inflammation and meniscal degeneration (4). KOA is the result of imbalance between catabolic and repair process; the main risk factor is aging, but the decay is accelerated by mechanical factors, such as lower limb malalignment and articular trauma, and systemic diseases, such as metabolic (diabetes, obesity...) or autoimmune (rheumatoid arthritis, ...) pathologies. These individuals are at higher risk of developing KOA at an earlier age, with more severe symptoms, though they could manifest after a long time from the "primum movens", as for radiographic

and macroscopic changes. Since there are no disease modifying drugs and patients eventually undergo total knee replacement, there is a rising interest in detecting and treating early stages of KOA (3).

Cartilage defects can cause significant disability and predispose to KOA. Severity correlates with thickness of articular damage: superficial lesions do not heal but often are poorly or not symptomatic at all, while full thickness defects usually heal forming fibrous cartilage but yielding more severe consequences (47). Patients with small lesions are more likely to be asymptomatic after restoration of cartilage, even though it's not hyaline tissue (23). Larger defects are usually a painful and limiting condition, leading to an impairment in joint homeostasis towards decaying process. In the long time, such lesions are going to yield the onset of KOA (22).

Several surgical treatments have been proposed to regenerate articular cartilage: microfractures, autologous chondrocyte implantation and osteochondral transplants.

Microfractures (MF)

Microfracture is the most widely used marrow-stimulation procedure. MF is usually performed with tapered awls with conical drill holes 0.5 to 1 mm in diameter, 4 mm deep, and approximately 3 to 4 mm apart. Holes are made in the lesion starting from the periphery to the lesion's center (5) to provide blood supply to the defect, with formation of a clot. Healing process evolves in fibrous cartilage formation.

It is often considered a gold standard treatment option for smaller and contained cartilage lesions given the ease and low cost of the procedure as well as the good short-term outcomes demonstrated with this procedure (6). Several studies show good outcomes improvement both in midterm and long term follow up (7-10).

Autologous chondrocyte implantation (ACI)

Autologous chondrocyte implantation is indicated for larger lesions according to many surgeons. It was initially performed as a 2-steps process in which the first procedure involves knee arthroscopic surgery with collection of a cartilage biopsy specimen (11). The location of the biopsy sample is taken from the margin of the trochlea. After the culture of autogenous chondrocytes, the second stage of the procedure involves knee arthrotomy for implantation of the expanded chondrocytes. This involves removal of a flap of periosteum from the patient's tibia and using it to cover the newly implanted chondrocytes (12). A new generation matrix-associated ACI (M-ACI) is now available. This procedure is similar, although rather than using a periosteal patch, chondrocytes are seeded on a hyaluronic acid-based scaffold to obtain the bioengineered tissue. This graft is positioned within the defect location, where it remains tightly adhered without necessitating fibrin glue or sutures to fix the implant (13, 14).

Osteochondral transplants

Reconstruction techniques, including osteochondral autograft transplantation as well as osteochondral

allograft transplantation (OAT), are surgical solutions that address both the cartilage and the osseous components of the injury. The autograft option is attractive in that it is a single-stage procedure that involves the harvest of osteoarticular plugs from a nonarticulating portion of the knee, followed by the placement of these plugs into the defect site; no foreign tissue is required (15). Given the need to use the healthy osteoarticular plugs from the patient, this technique may be best suited for smaller (≤ 2 cm²) lesions, and certainly, there is some concern over donor-site morbidity.

With advances in surgical instrumentation and expanding indications, OAT is being performed with increasing frequency. The benefits of OAT are many, including the ability to treat larger defects, lack of donor-site morbidity and reduced surgical time, and ability to customize the graft to the recipient's defect site. Further, many authors have reported good to excellent clinical outcomes after primary OAT, after OAT as a salvage procedure for failed prior cartilage restoration, and after OAT combined with meniscus allograft transplantation (MAT) (16-18).

However, some concerns over OAT remain, including cost concerns, unavailability of allograft tissue, and disease transmission. The overall complication rate after OAT is low (19); however, one of the more poorly understood complications after OAT is the need for reoperations.

Low friction, resistance to wear and absorption of stresses are mechanical properties required for a functional cartilage tissue. Benefits derived from these procedures are different, depending from the repair tissue obtained and strictly related to the technique used. MF is considered to produce a clot from subchondral bleeding, containing growth factors, but resulting in a fibrous cartilage, with poor mechanical properties. On the other hand ACI and OAT should produce a more hyaline-like tissue, at a cost of a higher invasivity. However, differences in cartilage quality seems not to affect clinical results (20). Several randomized studies compared the treatments mentioned above, mainly MF and ACI (20-24). Independently from the treatment, were it MF or ACI or OAT, patients outcomes were similar, with no statistically significant difference in clinical scores and failure rates. Furthermore, Knutsen et al (20) found out no

difference in histological quality of repair tissue in patients with or without a failure of treatment. For these reasons, lack of blood supply and low metabolic potential, that should protect cartilage in a healthy joint environment, are believed to compromise the success of surgical treatments, whatever it is, and joint replacement is often ultimately required. Moreover, biologic response to treatments correlates with “age” of the lesions: patients who are symptomatic for a longer time are less likely to benefit from any intervention (21). For these reasons, thanks to a deeper knowledge about biologic processes, methods to enhance cellular response are developing. The two main sources of biological support, used to provide hyaline cartilage restoration, were identified in platelet-rich plasma and mesenchymal stem cells.

PRP

Platelet-rich plasma (PRP) is derived from a sample of autologous blood prepared until its concentration of platelets is above base-line values. It is theorized that higher levels of platelets can allow for release of growth factors, which may promote angiogenesis and soft tissue healing. Results have indicated a beneficial effect of PRP on chondrocytes and mesenchymal stem cells. PRP also promotes differentiation of subchondral bone progenitor cells. Kruger et al. not only demonstrated that PRP significantly stimulated the migration of human progenitor cells in chemotaxis assays, but also showed that histological staining revealed increased cartilage matrix formation in cells treated with PRP compared with untreated progenitor controls (25). Furthermore, Anitua et al. reported that synoviocytes from patients with osteoarthritis (OA) cultured in PRGF demonstrated an increase in hyaluronan (HA) production. The authors proposed that intra-articular administration of PRP might be beneficial in restoring hyaluronic acid concentration and serve as an endogenous source of chondroprotection and joint lubrication. The inconsistent results between studies, however, demonstrate that, although the groundwork is laid, the true efficacy of PRP is yet to be determined. In addition to variation of blood cell components contained within each product, an indi-

vidual’s health, age and comorbidities may also reflect the effectiveness of PRP (26).

MSCs

Mesenchymal stem cells (MSCs) are multipotent cells present in the stroma of many human organs and tissues. The best source of adult MSCs remains unclear. Several different tissues have been explored including bone marrow, adipose tissue, and umbilical cord tissue (Wharton’s jelly). Traditionally bone marrow has been used as a source of MSCs, though research has shown a relative paucity of MSCs within bone marrow aspirates (BMA) comprising only .001-.02% of mononucleated cells isolated from aspirates (27, 28). In comparison, human adipose tissue through a lipoaspirate procedure, yields MSC numbers of ~1-7% of the nucleated cell population (29). Its ease of harvest and the relative abundance of MSCs in adipose tissue has seen this method increasingly used for autologous therapies.

Indeed, Adipose-derived MSCs (ASCs) can be easily obtained by a minimal invasive surgical procedure and expanded *in vitro*. In addition, ASCs have been shown to possess strong regenerative properties when transplanted *in vivo* in experimental animal models (30, 31). and this potential may be used to regenerate damaged tissues. In addition, MSCs secrete a variety of bioactive molecules that act in a paracrine way to prime and sustain angiogenic, antifibrotic, antiapoptotic, and immunomodulatory responses in target tissue (32). Adipose-derived MSCs routinely are obtained enzymatically from fat lipoaspirates (LP) and may undergo prolonged *ex vivo* expansion, with significant senescence and a decline in multipotency. In addition, the technique is fraught with complex regulatory issues. For these reasons, Tremolada and colleagues (33) recently developed an enzyme free technology able to obtain a micro-fragmented fat preparation containing a significant number of Ad-MSCs. Adipose tissue is the ideal source for extracting MSCs because it can be easily accessed and harvested via a minimally invasive surgical procedure, it may be found in large quantities in most people, and it guarantees an adequate amount of stem cells with good viability and age-related differentiating potential.

Discussion

Actual surgical treatments for osteochondral lesions and early knee osteoarthritis seem to be promising. Microfractures, are often considered the first-line surgical treatment option due to the low costs and ease of the technique (34-38), while ACI is rather reserved as a salvage procedure (39-41, 45).

On the other hand, MF are supposed to have long-term limits in clinical outcome, related to the poor biomechanical characters of fibrous cartilage, though evidence provided by literature reports no significant differences (20-24).

OAT, ACI and MACI techniques are widely used in the clinical practice and showed good results in the mid and long-term follow-up. However, the costs and the unavailability of allograft tissue in all centers make these techniques more difficult to perform if compared to the microfractures.

Biological derivatives, such as platelet-rich plasma and mesenchymal stem cells, have been introduced in clinical practice to improve the quality of regenerative tissue (42).

Many studies on PRP have been conducted, however, the true efficacy of this technique alone is yet to be determined. Growth factors could have contradicting roles, depending on the *in vivo* model used. For example, in the work of 2013 Ellman et al, found out FGF-2 accelerates spontaneous and induced OA development in humans, whereas in murine model it has a chondroprotective action (43). In addition to the variation of blood cell components contained within each product, individual's health, age and comorbidities may also reflect the effectiveness of PRP, so actual results are still inconsistent.

Natural and physical therapies have been used in orthopaedics and traumatology (44, 45). Gang-Hua Cui and coll. recently published a meta-analysis on the efficacy of MSCs treatment in KOA (46). They concur that MSC treatment seem to significantly improve pain and function and the effectiveness do not reduce over time. The optimal dose and vehicle are yet to be established. However, in the last years there has been a greater interest in the adipose-derived MSC treatment due to its ease of harvest and availability of adipose tissue. This technique seem to collect higher MSCs

concentrations and to yield superior results. Further control studies will be necessary to confirm these preliminary results of treatments with MSCs and their biological action.

Conclusions

In conclusion, treatment of early knee osteoarthritis and chondral lesions is still a challenging problem. Current surgical treatments, such as microfractures, ACI and OAT, are the best options available, though it could be hard to increase the use of ACI and OAT because of similar results and higher costs, if compared with MF. Biological augmentations could be the solution to enhancing the outcomes of a simple technique. PRP seems to be promising but true efficacy is yet to be determined. The attention is recently focused on the more encouraging results on MSCs and ASCs. Nevertheless large cohort studies with long term follow-up are needed to understand the biological action and the real benefits of this techniques."

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Correspondance:

Carlo Dall'Oca, MD

Clinica Ortopedica,

Azienda Ospedaliero Universitaria Integrata,

Verona

E-mail: carlodalloca@univr.it