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Emergence of Orthobiologics as a Novel Therapeutic Modality for Osteoarthritis of Knee

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Abstract

Osteoarthritis [OA] of knee is a common cause of disability worldwide. The number of non-operative treatment options is on the rise. Orthobiologic therapy has emerged as a novel yet effective modality for early OA. It aims at achieving biologic repair, by repairing the damaged joint surface with autologous articular cartilage. Exploiting the healing and rejuvenating properties of body's own cells for the repair and renewal of damaged tissues is the basic crux behind orthobiologic therapy. Creation of an ambient structural, biological and biomechanical environment is an essential prerequisite for successful orthobiologic therapy. There are a number of orthobiologic options - platelet rich plasma (PRP), bone marrow concentrate (BMC), adipose tissue derived mesenchymal stem cells (ADMSC), autologous chondrocyte implantation (ACI) and autologous conditioned serum. This review article discusses the clinical indications, rationale, preparation, pros and cons of each one of them in detail along with a comprehensive review of published literature.

Keywords: Orthobiologics; Osteoarthritis; Knee; Cartilage; Total knee arthroplasty

Introduction

Osteoarthritis (OA) of knee is one of the most common clinical scenarios presenting in an orthopaedic clinic. In OA, the aging cartilage fails to produce enough inhibitors to curtail the ongoing degenerative process. In addition, the regenerative capabilities of the innate chondrogenic progenitor cells are not up to the mark in a worn out avascular cartilage tissue [1]. Chondrocytes have a poor response to injury characterized by a transient, limited increase in their mitotic activity. Instead of a functional hyaline cartilage, the reparative processes culminate in the production of a fibrocartilage which is incompetent in enduring biomechanical loads over time. Hence, intrinsic self-repair abilities of the diseased cartilage of a weight bearing joint are not efficient enough either to halt the disease progression or to reverse their vicious course [1,2].

Majority of the cases presenting with painful disabling advanced OA clearly benefit from total knee arthroplasty (TKA). There are a number of non-operative options for those presenting early. The routine choices include non-steroidal anti-inflammatory drugs (NSAIDS), muscle relaxants, physiotherapy, knee braces, life style modification, chondroprotective agents (diacerein, glucosamaine, chondroitin sulphate), viscosupplementation i.e. intra-articular hyalyuronic acid (HA). Recently the efficacy of Orthobiologic agents has been reported in the literature [3].

Orthobiologic therapy is the sword wielded by the emerging era of regenerative medicine to combat numerous musculoskeletal ailments including degenerative OA [4]. Of late, orthobiologics have evolved as one of the prominent treatment modalities for early osteoarthritis (OA) of the knee. Unabated interests and incessant research in the field of regenerative medicine, coupled with promising clinical results from the use of orthobiologics are diversifying the clinical applications of this "cutting-edge" biological treatment day by day. Biological therapy or in other words, "cellular arthroplasty" is evolving as a new paradigm in the management of OA. Exploiting the healing and rejuvenating properties of body's own cells for the repair and renewal of damaged tissues is the basic crux behind orthobiologic therapy. Repair of damaged cartilage and biological restitution can be possible by the judicious use of autologous biological products. In the treatment of OA, orthobiologics occupy an intermediary position between the non-invasive conservative management at one end and the more invasive surgical options at the other end. The innovative biological options which have been successful in the management of osteoarthritis include platelet rich plasma (PRP), bone marrow concentrate (BMC), adipose tissue derived mesenchymal stem cells (ADMSC), autologous chondrocyte implantation (ACI) and autologous conditioned serum. The clinical role of these orthobiologics in the management of knee OA along with their potential merits and demerits has been discussed in detail along with a comprehensive up-to-date review of published literature. This review predominantly focuses on contemporary autologous biologic agents that are being used for the clinical treatment of OA knee. However, this review does not include in vitro or animal studies, those studies involving allogenic or synthetic agents and those studies focusing on isolated chondral pathologies rather than generalized OA.

Platelet Rich Plasma

Autologous plasma containing a platelet count 4-5 times above baseline is termed as PRP. Synonyms include plasma rich in growth factors (PRGF), platelet enriched plasma (PeRP), platelet abundant plasma (PAP), platelet rich concentrate (PRC) and autologous platelet gel [5]. The potent concentration of platelets are administered to stimulate a supra-physiologic response, as they are comprised of an undifferentiated cocktail of anti-inflammatory, pro-inflammatory,

anabolic, and catabolic mediators in an attempt to elicit the body's natural healing response [4].

The alpha granules of the platelet are rich in alluring growth factors. These include transforming growth factor-beta (TGF β), epidermal growth factor (EGF), platelet derived growth factor (PDGF), fibroblast growth factor (bFGF), Insulin like growth factor (IGF-1), stromal derived factor 1 alpha, bone morphogenic protein (BMP-2) and many other factors. All the biological actions of PRP are mediated by these growth factors. Cumulative array of these growth factors possess unique multitasking abilities which include promotion of cellular chemotaxis, proliferation and differentiation, removal of tissue debris, angiogenesis and the laying down of extracellular matrix [5]. TGF β, IGF, bFGF and PDGF are chondroprotective [6]. These bioactive proteins establish their chondroprotective role by not only stepping up the chondrocyte anabolism, but also, by hampering the catabolic inflammatory cascade. IGF-1 plays a vital role in orchestrating the homeostasis of articular cartilage. It enhances cartilage repair by not only promoting synthesis of aggrecan, link protein, and hyaluronan, but also by inhibiting proteoglycan degradation [7]. PDGF and TGF-1 are believed to up-regulate the production of endogenous hyaluronic acid levels [8]. PRGF is also believed to be capable of regulating the levels of tissue inhibitors of metalloproteinases (TIMP).

The fibrinogen content of PRP further increases its biological efficacy by forming a fibrin scaffold after activation and helps in tissue healing by filling up cartilage defects. Thus the mechanism of action of PRP can be broadly summed up to its functional components: (I) growth factors - steering up the cellular anabolism, (II) inflammatory modulators - triggering counter-inflammatory responses and (III) fibrinogen-acting as a biomaterial scaffold [6].

PRP is prepared from 50-60 ml of the patient's blood into a bag containing an anticoagulant, and centrifuged for 15 minutes at 1,500 rpm on a table-top centrifuge. The blood components settle down in three distinct layers. The bottom layer is comprised of red blood cells, the middle of platelets and white blood cells (buffy coat), and the top of plasma. The platelet rich plasma (PRP) is extracted through a pipette and transferred to a test tube. The PRP yield is approximately 10% of the volume of whole blood drawn. It is then passed through a leucocyte filter and about 8 ml of PRP is used in each knee. It is activated so as to facilitate the release of α- granules from the platelets into the gel thus formed for direct application [5,9]. The calcium chloride required for activation is given in a separate syringe in a ratio of 4:1(Figure 1). To confirm sterility of PRP, culture - sensitivity was performed. The entire procedure is done under complete aseptic precautions [5,9].

The relative feasibility of PRP preparation is complemented by its alluring clinical safety profile. Being a completely autologous product, PRP negates the chances of disease transmission and plausible immunogenic reactions that can occur with other products such as the avian derived hyaluronic acid viscosupplements [5]. Another merit worth mentioning is the ability to perform the whole process starting from blood sample collection till intra-articular PRP instillation as a daycare procedure, thus obviating the need for any hospitalization or sophisticated operative theatre requirements. Overall, PRP therapy for OA knee is relatively simple, economical and minimally invasive.

Apart from OA knee, PRP has also been successfully employed in a number of musculoskeletal conditions. These include tendinopathies (rotator cuff, lateral epicondyle, patellar, achilles), ligament tears (ACL), plantar fasciitis and non-unions [10]. PRP has been used in patients of early osteoarthritis in an attempt to improve the cartilage structure and to slow down the progression of the disease.

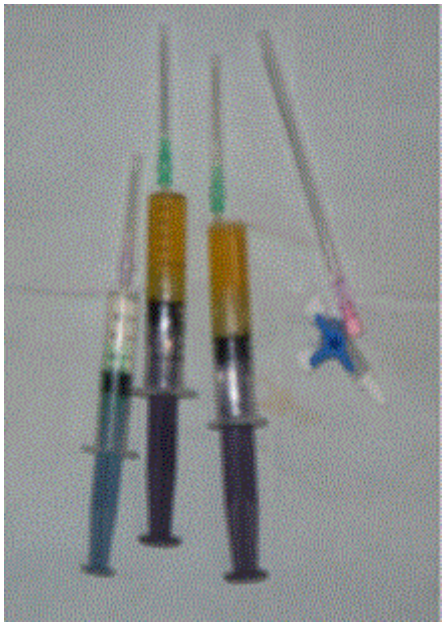

Figure 1: Syringes containing platelet rich plasma and calcium chloride and a three-way cannula and a spinal needle.

PRP - Evidence based medicine

There are a number of studies proving the clinical efficacy of PRP.

In 2010, Sampson et al. [11] conducted a prospective pilot study on 14 patients with OA knee by administering 3 intra-articular PRP injections at 4 weekly intervals. Significant improvement was observed in Knee Injury and Osteoarthritis Outcome Scores, including pain and symptom relief. The majority of the patients expressed a favorable outcome at 12 month follow up. In 2011, Wang-Saegusa et al. [12] treated 312 patients with knee OA [Outerbridge I-IV], who were symptomatic for more than 3 months, with 3 intra-articular injections of PRGF at 2 weekly intervals. Significant improvement in pain, stiffness and function was observed at 6 month follow up. However, this study was a level IV case series and there was no control group.

The following studies establish the supremacy of PRP over HA for OA knee:

In 2011, a randomized controlled trial (RCT) involving 150 patients with early OA by Kon et al. [13] compared the clinical outcome after intra-articular PRP versus low and high molecular weight HA in three patient groups. PRP was found to provide longer and better efficacy in reducing pain and symptoms, than both low molecular weight HA and high molecular weight HA on a6 month follow up. In another RCT by Spakova et al. [14] in 2012, 60 cases with OA (Kellgren and Lawrence grades 1, 2, or 3) received PRP and 60 matched controls received HA. The pain score and the WOMAC score were statistically better in the PRP group at 6 month follow up. In a similar RCT published in the same year by Cerza et al. [15] on 120 OA knees, there was significant reduction in the WOMAC scores in the PRP group and the effect sustained up to 24 weeks. In the same year, Sanchez et al. [16] conducted a multicenter, double-blinded clinical trial to evaluate the safety and efficacy of 3 consecutive weekly intra-articular PRGF versus HA injections in 176 patients. PRGF was found to be superior to HA in alleviating knee symptoms in mild to moderate OA.

The following study establishes the supremacy of PRP over a placebo:

In 2013, Khosbin et al. [17] conducted a systematic review of 577 patients included from six level I and level II studies to evaluate the clinical efficacy of PRP versus a control injection for knee OA. The therapeutic effect was evaluated using validated outcome measures - WOMAC index, VAS score, International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form and overall patient satisfaction. They concluded that compared with HA or NS injection, multiple sequential intra-articular PRP injections may have beneficial effects in the treatment of adult patients with mild to moderate knee OA at approximately 6 months. However, PRP is less effective for those with severe OA.

Filardo et al. [18] conducted a systematic review to analyze the role of intra-articular PRP in the treatment of cartilage lesions and joint degeneration. They concluded that an intra-articular PRP injection did not just target cartilage; instead, PRP might influence the entire joint environment, leading to a short-term clinical improvement. They also added that there might be multiple biological variables which might influence the clinical outcome.

In 2014, Anitua et al. [19] conducted a systematic review of international peer reviewed literature published between 2008 and 2013 on the efficacy and safety of plasma rich in growth factors (PRGF) in knee OA. A total of 530 patients were included from 5 different studies - 2 were randomized controlled trials (RCTs), 2 were prospective studies and 1 was a retrospective analysis. They concluded that intra-articular PRGF significantly reduced pain and improved function in patients with mild to moderate knee OA.

PRP - Areas of concern

Filardo et al. [20] reported the incidence of pain and swelling with the use of leucocyte enriched PRP. These adverse effects are attributed to the transient inflammatory process triggered by the leucocytes inside the synovial joint [21]. Leucocytes are thus better avoided in PRP preparations [19]. Other less common but reported adverse effects of PRP include injection related [infection, neurovascular injury, scaring, calcification], hypersensitivity reactions [if bovine origin thrombin is used for platelet activation] and even rarely, development of auto-antibodies to factor V and IX resulting in fatal coagulopathies [20].

Antiplatelet drugs inhibit platelet function especially impairing the release of growth factors from its granules, thus rendering PRP ineffective. Chronic anti-platelet therapy is considered as a contra-indication for the clinical use of PRP [16,22,23]. Di Matteo et al. [24] reported successful use of PRP in a patient who was on chronic platelet anti-aggregant therapy. The patient was totally pain free and resumed physical activities without any disability. Nevertheless, further research is needed to advocate the use of PRP in Patients who are on anti-platelets.

In 2010, Kon et al. [23] conducted a prospective study on 100 consecutive patients (115 knees) with OA knees which included 58 knees with degenerative chondral lesion (Kellgren 0), 33 with early OA (Kellgren I-III) and 24 with advanced OA (Kellgren IV). Three intra-articular PRP injections were administered at 3 weekly intervals and followed with EQVAS and IKDC scoring at 6 and 12 month follow up. Statistically significant improvements of all scores were noted at 6 month follow up; but, at 12 months, the scores worsened. In 2012, Filardo et al. [25] prospectively evaluated 109 patients with OA knee (Kellgren-Lawren I-III) receiving three weekly injections of PRP (54 patients) and HA (55 patients). Even though there was significant clinical improvement in the PRP group upto one year follow up, the comparison between the two groups did not show a statistically significant difference in all the scores (IKDC, EQ-VAS, TEGNER, and KOOS) evaluated. The authors concluded that, for middle-aged patients with moderate signs of OA, PRP did not offer better results compared to HA, contrary to the available literature, and thus it should not be considered as first line treatment [24]. The variability in the clinical results of PRP may be at least partly attributed to the differences in equipment, preparation, cell content, platelet concentration technique, activation methods, timing of injections, etc. leading to a high inter-product variability.

Importance of Autologous Biologic Agents

Sheth et al in 2012 conducted a Meta- analysis to determine the efficacy of autologous Platelet-Rich Plasma use for orthopaedic indications [26]. They identified 23 randomized trials and 10 prospective cohort studies. In six randomized controlled trials (n=358) and three prospective cohort studies (n=88), the authors reported visual analog scale (VAS) scores when comparing platelet-rich plasma with a control in various Orthopaedic conditions such as injuries to the acromion, rotator cuff, lateral humeral epicondyle, anterior cruciate ligament, patella, tibia, and spine. The use of platelet-rich plasma provided no significant benefit up to (and including) twenty-four months across the randomized trials (standardized mean difference, 20.34; 95% confidence interval (CI), 20.75 to 0.06) or the prospective cohort studies (standardized mean difference, 20.20; 95% CI, 20.64 to 0.23). Both point estimates suggested a small trend favoring platelet-rich plasma [26].

Bone marrow concentrate

Mesenchymal stem cells [MSC] are responsible for auto-repair after tissue injury. MSCs are multipotent and are involved in regeneration of many mesenchymal tissues including cartilage. They can be isolated from many sources including bone marrow, adipose tissue, umbilical cord blood, amniotic fluid, Wharton's jelly, dental pulp, peripheral blood, skin, trabecular bone of mandible, skeletal muscle, synovial membrane and synovial fluid [27]. The chondrogenic potential of adult stem cells can be enhanced by the addition of chondro-inductive agents like TGF- β and BMPs [28]. However, their chondrogenic potential varies according to their source. Li et al. [29] showed that the in vivo chondrogenic potential of MSCs originating from the bone marrow is greater than those derived from adipose tissue, synovium, periosteum and muscle.

The chondrogenic potential of bone marrow derived stem cells (BMSCs) can be clinically harnessed by administering them either as pure BMSC after in vitro isolation or as BMC in toto. BMC contains a bioactive blend of BMSCs, hematopoietic cells, platelets, immunomodulatory cytokines and various growth factors. The probable mode of action is hypothesized to be either due to activation of resident stem cells or due to inherent chondrogenic potential. The anti-inflammatory and immunomodulatory properties of bone marrow stem cells can facilitate regeneration of tissue. Additionally, BMSCs enhance the quality of cartilage repair by increasing aggrecan content and tissue firmness [30].

Kim et al. [31] evaluated the clinical efficacy of intra-articular injection of BMC with adipose tissue in 41 patients [75 knees] with OA [Kellgren-Lawrence I-IV]. There was improvement in both the pain score [VAS] and the functional scores [IKDC, SF-36, KOOS, Lysholm Knee Questionnaire] at 3, 6 and 12 month follow up. BMC was found to be more effective in early to moderate OA. In a longitudinal study

by Centeno et al. [32], the safety, efficacy and differences between two stem cell therapies for OA knee - BMC alone versus BMC with addition of adipose derived lipoaspirate, were evaluated. A total of 840 knees were treated in 681 patients - 518 patients in the first group and 163 patients in the later. They concluded that BMC injections for knee OA showed encouraging outcomes and a low rate of adverse effects. Addition of an adipose graft to the BMC did not provide a detectible benefit over BMC alone. Pain/swelling was the most commonly reported adverse event. This was generally self-limited and resolved without any intervention.

When compared to pure BMSC preparation, BMC is relatively easier to prepare. It does not need sophisticated laboratory set up to isolate and expand BMCs. It can be transplanted in a one-step operative procedure. The whole process is cheaper than a two-step BMSC therapy.

Bone marrow derived stem cells (BMSC)

This form of therapy utilizes the cartilage healing and renewal properties of a sole component derived from bone marrow - BMSC. Treatment involves a two-step process. First, the bone marrow is harvested. Then, the BMSCs are isolated and expanded over serial culture passages in vitro in a laboratory. Once their number reaches between 3.8×10^6 and 11.2×10^6 cells/ml, they are surgically transplanted to the target site with the help of a scaffolding collagenic or hyaluronic acid membrane. Cartilage defects that can be repaired by this two-step technique are about twice the size as those where the one-step method (BMC) is used [33].

In 2002, Wakitani et al. [34] compared two groups of patients of 12 patients each with OA knee who underwent high tibial osteotomies. One group received BMSC and the other group served as a control. On follow up, there was significant improvement in the BMSC group-arthroscopically and histologically, but not, clinically. Centeno et al. [35] showed that percutaneous injection of BMSCs into a knee with symptomatic and radiographic degenerative joint disease resulted in significant cartilage growth, decreased pain and increased joint mobility.

Emadedin et al. [36] reported satisfactory improvement in pain and functional status after intra-articular injection of MSCs in six patients with knee OA. The follow up MRI of three out of six patients at 6 months follow up demonstrated an increase in cartilage thickness, extension of the repair tissue over the subchondral bone and a considerable decrease in the size of edematous subchondral patches. In another clinic-radiological pilot study, Orozco et al. [37] treated 12 patients with OA knee with intra-articular BMSCs injection and evaluated their clinical and radiological (MRI) outcome at 1 year follow up. There was significant improvement both clinically - improvement in pain, disability and quality of life, and, radiologically - highly significant decrease of poor cartilage areas along with improvement of cartilage quality in 11 of the 12 patients.

Autologous BMSCs are thought to be safe because of the absence of immunological reaction and disease transmission. In 2011, Wakitani et al. [38] established the long term safety profile of BMSC in the treatment of OA knee. On following up a group of 41 patients over a mean of 75 months (range: 5-137 months), neither tumours nor infections were observed. The safety profile of MSCs was also highlighted by a systematic review conducted by Peters et al. [39] in 2013. The authors declared the safety of intra-articular stem cell therapy after studying the adverse effects of MSCs treatment from 8 different studies involving a total of 844 intra-articular procedures.

Adipose Derived MSC (ADMSC)

ADMSCs are easy to procure than BMSCs. Moreover, they can be procured in larger quantities with standard liposuction methods which are comparatively far less invasive than those involved in the harvesting of BMSCs. The common harvesting sites include the adipose tissue of abdomen, thigh and hips. ADMSCs are a type of multipotent adult stem cell with promising chondrogenic potential. The response of ASCs to growth factors and biomaterial scaffolds may differ significantly from BMSCs [40]. They have enhanced rates of proliferation, but lesser responses to TGF-ß induced chondrogenesis [4].

In a case series, Koh et al. [41] evaluated the clinical and imaging results of 18 patients who received intra-articular injections of ADMSC [infrapatellar fat pad-derived] for the treatment of knee OA. After a mean follow up of 24.3 months, significant improvement was observed not only in both pain (VAS) and functional scores (WOMAC and Lysholm), but also, in MRI (cartilage whole-organ MRI score). The authors also showed that improvements in clinical and MRI results were positively related to the number of stem cells injected. In another study, Jo et al. [42] evaluated the safety and efficacy of intra-articular injection of ADMSC in 18 patients with OA knee. The 6 month follow up results showed that intra-articular injection of 1.0×10^8 ADMSCs improved pain and function (WOMAC) without causing adverse events, and reduced cartilage defects by regeneration of hyaline-like articular cartilage.

There are a few limitations of ADMSCs. Optimal in vitro culture period is still under research. There is a theoretical chance of tumorigenesis in view of the extensive cell expansion in culture. However, Pak et al. [43] demonstrated no evidence of neoplastic complications in a study involving 91 patients (100 joints) who received a combination of ADMSC along with PRP.

To date, there is a paucity of level I evidence evaluating the therapeutic efficacy of BMC, as many of the studies are non-randomized, lack a control, and present only observational results of case series. The number of cases in the study group is small. Properly powered clinical trials, appropriate clinician collaboration and further follow-up on the use of ADSCs and UCDCs are essential. Many queries remain polemical such as the ideal cell harvest technique, cell preparation as well as optimal window for various indications and injection protocols [1]. Moreover, the quality of stem cells and their chondrogenic potential may be affected by the presence of coexisting confounding factors like increased age and obesity, both of which are independent risk factors for OA [28].

Peripheral Blood Stem Cell [PBSC]

In a RCT published in 2013, Saw et al. [44] compared the histologic and MRI evaluation of articular cartilage regeneration in fifty patients with chondral lesions [International Cartilage Repair Society (ICRS) grade 3 and 4 lesions of the knee joint] treated by arthroscopic subchondral drilling followed by postoperative intra-articular injections of HA with and without PBSC. Their results showed that intra-articular injections of autologous PBSC in combination with HA resulted in an improvement of the quality of articular cartilage repair over the same treatment without PBSC, as shown by histologic and MRI evaluation.

In a case series involving 5 patients with early OA knee, Turajane et al. [45] evaluated the combination of repeated intra-articular (IA) autologous activated PBSC with growth factor addition/preservation (GFAP) along with HA in conjunction with arthroscopic microdrilling

mesenchymal cell stimulation (MCS). There was a significant improvement in WOMAC and KOO scores at one and six months follow up. Histological analysis of cancellous bone biopsies on follow up, demonstrated increased proteoglycan and glycosaminoglycan content indicating presence of hyaline cartilage.

Autologous Chondrocyte Implantation (ACI)

Injury to an articular cartilage and subchondral bone triggers a cascade of reparative processes which culminates in the production of biomechanically inferior fibrocartilage, which eventually fails on repetitive loading. Orthopaedic procedures like arthroscopic debridement, drilling, abrasion chondroplasty, microfracture and use of carbon fibre pads, induce a fibrocartilaginous repair mechanism. ACI aims at achieving biologic repair, by repairing the joint surface with autologous articular cartilage. The formation of hyaline or hyaline-like cartilage may be induced by implanting autologous, cultured chondrocytes into the chondral or osteochondral defect [2].

In this technique, the autologous cells are harvested from a non weight bearing region of the articular cartilage, for example, medial edge of trochlear groove. The chondrocytes are isolated and expanded in culture ex vivo over a 4- to 6-week period after which they are implanted at the target site. Pertinent care must be taken to ensure the safety, viability, and microbial integrity of the autologous cells during the process of harvest, transport and storage. Surgical implantation requires equal attention to meticulous technique [46,47]. Initially, the ACI technique utilized autologous periosteum to form a watertight cover under which the chondrocyte suspension was injected. Later, synthetic collagen was used as a patch [collagen patch ACI or C-ACI) with clinical outcomes similar to ACI. The promising advent of ACI lead to the emergence of matrix induced autologous chondrocyte implantation (MACI). Here, the cultured chondrocytes are directly seeded onto a type I/III collagen scaffold which not only acts a carrier but also ensures even distribution of cultured chondrocytes [2,48].

Autologous chondrocyte implantation may be used for symptomatic full-thickness chondral or osteochondral injuries. An ACI should be considered for symptomatic patients with a lesion of between 1 cm^2 and 12 cm^2 and for those whose previous treatment, such as microfracture and mosaicplasty, has failed. Reciprocal or 'kissing' lesions are a contraindication to ACI. Gikas et al. [2] showed that ACI leads to a statistically significant improvement in objective and patient-reported clinical outcome scores and produces a durable outcome for as long as nine years. Minas et al. [47] and Brittberg et al. [49] showed that ACI brought about significant improvement in pain, swelling and function after surgery.

There are certain limitations of ACI. The treatment is relatively costly. Donor site morbidity should not be forgotten. The patient has to undergo two surgical procedures. The whole process is technically demanding both surgically and laborartory wise. A well equipped sophisticated laboratory set up is necessary for in vitro studies. The in vitro cultured chondrocytes may de-differentiate. There might be variability in the biological response of the periosteal flap. The periosteal flap may detach, delaminate or undergo late hypertrophy [50].

Conclusion

To summarize, the clinical utility of biological restoration of the articular milieu can be optimized by understanding the basic underlying pathology. Articular cartilage cannot be restored in isolation. OA can be viewed as an overt manifestation of the failure of synovial joint of the knee as an organ. Therefore, a holistic approach has to be advocated which addresses all the pathologic tissues of the knee "organ" in toto. Creation of an ambient structural, biological and biomechanical environment is an essential prerequisite for successful Orthobiologic therapy. Structurally, OA is a multifaceted disease involving not only the hyaline cartilage, but also, the synovium, fibrous capsule, meniscus and the subchondral bone. Pathologically, myriad pathogenic factors are involved, such as, extracellular matrix-degrading enzymes, inflammatory and anti-inflammatory cytokines. Biomechanically, limb malalignment, ligamentous insufficiency, muscular imbalance and instabilities must be taken care of [1,48]. Even though there has been a substantial increase in our understanding over the past few decades about the role of orthobiologics in the management of OA knee, research is yet to identify an ideal biological agent which can not only restore the three dimensional structure of the native cartilage but also be competent enough to withstand physiological loading forces efficiently over time. In other words, future rejuvenative research should be aimed at simultaneous biological and biomechanical restoration of the articular homeostasis. Among the available Orthobiologic options, PRP is rising as a new avenue in the management of early OA knee. MSC and ACI therapy can also be promising, if future research is able to encourage adequate randomized clinical studies and circumvent the technical feasibilities associated with their use.

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