**Level V Evidence**

# Nonoperative and Operative Soft-Tissue and Cartilage Regeneration and Orthopaedic Biologics of the Knee: An Orthoregeneration Network (ON) Foundation Review

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**Abstract:** Orthoregeneration is defined as a solution for orthopedic conditions that harnesses the benefits of biology to improve healing, reduce pain, improve function, and optimally, provide an environment for tissue regeneration. Options include: drugs, surgical intervention, scaffolds, biologics as a product of cells, and physical and electro-magnetic stimuli. The goal of regenerative medicine is to enhance the healing of tissue after musculoskeletal injuries as both isolated treatment and adjunct to surgical management, using novel therapies to improve recovery and outcomes. Various orthopaedic biologics (orthobiologics) have been investigated for the treatment of pathology involving the knee, including symptomatic osteoarthritis and chondral injuries, as well as injuries to tendon, meniscus, and ligament, including the anterior cruciate ligament. Promising and established treatment modalities include hyaluronic acid (HA) in liquid or scaffold form; platelet-rich plasma (PRP); bone marrow aspirate (BMA) comprising mesenchymal stromal cells (MSCs), hematopoietic stem cells, endothelial progenitor cells, and growth factors; connective tissue progenitor cells (CTPs) including adipose-derived mesenchymal stem cells (AD-MSCs) and tendon-derived stem cells (TDSCs); matrix cell—based therapy including autologous chondrocytes or allograft; vitamin D; and fibrin clot. Future investigations should standardize solution preparations, because inconsistent results reported may be due to heterogeneity of HA, PRP, BMAC, or MSC preparations and regimens, which may inhibit meaningful comparison between studies to determine the true efficacy and safety for each treatment.

The goal of regenerative medicine in orthopaedic surgery is to incorporate solutions aimed at enhancing musculoskeletal healing and or modify symptoms after injury or degeneration to reduce pain and improve function by modulating the biologic environment to promote tissue restoration.[1] The use of these techniques seeks to improve symptoms either by augmenting the healing of tissues that possess relatively poor intrinsic healing capabilities, including cartilage, menisci, tendon, and ligament, or by inhibiting biochemical pathways that might be associated with symptom generation.[1] Orthobiologic therapies are current used for the treatment of symptomatic focal chondral defects,[2,3] osteoarthritis (OA),[4-7] meniscal

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repair,[8-11] and tendon and ligament injuries.[12-14] Despite promising basic science data demonstrating the strong potential of multiple therapies, limited clinical data currently exist to support the use of these techniques.[1]

The potential utilization of orthobiologics to help restore function and accelerate recovery is of increasing interest to both patients and surgeons. Since 2017, the Orthoregeneration Network (ON) has served as an independent, international, nonprofit foundation driving development and understanding of new treatment options in the field of orthopaedic tissue regeneration. Orthoregeneration is defined as a solution for orthopedic conditions that harnesses the benefits of biology to improve healing, reduce pain, improve function, and optimally, provide an environment for tissue regeneration. Options include: drugs, surgical intervention, scaffolds, biologics as a product of cells, and physical and electro-magnetic stimuli.[15] The mission of the ON is to provide guidance, education, and knowledge for surgeons to improve the use of tissue regeneration and biologic therapies in clinical practice. The purpose of this review is to summarize the current status of orthoregenerative therapies for orthopaedic issues related to the knee.

## Overview of Orthoregeneration in the Knee

Cartilage possesses a poor inherent capacity for healing following injury. Partial-thickness cartilage lesions have no intrinsic reparative capacity, whereas a full-thickness defect that exposes bone will heal with biomechanically inferior fibrocartilage.[16,17] As a result, orthobiologic treatments are aimed at the treatment of focal articular chondral defects[18] and generalized OA.[4-7,19-21] Similarly, the meniscus has poor intrinsic healing potential for lesions in the inner, avascular zone, leading to interest in the role of orthobiologics for the treatment of meniscal injuries, as well as to augment meniscal repair, owing to the challenges associated with meniscal healing.[22,23] Orthobiologics have also been reported as an alternative and an adjunct treatment for tendon and ligament pathology.[24]

Hyaluronic acid (HA) is a high molecular weight glucosamine generated by native chondrocytes, providing viscoelasticity and lubrication within the knee joint.[25] In the arthritic knee, the concentration of HA has been reported to be decreased by 33% to 50% of normal levels.[26,27] HA injections are believed to mechanistically improve symptoms through a variety of mechanisms in addition to stimulating the production of HA from chondrocytes and synoviocytes, providing lubrication properties to protect the cartilage against mechanical stresses and potentially protecting against further chondral damage.[26,28]

Platelet-rich plasma (PRP) consists of harvested autologous blood concentrated through centrifugation to contain a minimum of 1.5- to 9-fold greater concentration of platelets compared with baseline serum levels.[29,30] PRP injections have been shown to stimulate platelet activation, leading to the release of various cytokines, growth factors, and inflammatory mediators and immune-modulating proteins, facilitating tissue healing by suppressing inflammation while promoting collagen synthesis, cell proliferation, and differentiation.[31-34]

Bone marrow aspirate (BMA) as well as bone marrow aspirate concentrate (BMAC) effectively deliver mesenchymal stromal cells (MSCs), hematopoietic stem cells, endothelial progenitor cells, and various growth factors.[35] BMAC has been shown to express strong regenerative properties for the treatment of chondral injuries, owing to the secretion of growth factor and cytokines from the surrounding tissues.[36] BMAC has been shown to increase chondrocyte proliferation and MSC differentiation, while aiding in wound healing and anti-inflammation by suppressing pro-inflammatory cytokines.[37]

Many tissues contain a population of connective tissue progenitor cells (CTPs) that are characterized by the potential to undergo self-renewal, differentiating into various cell lines.[38] CTPs have also demonstrated immune-suppressive and anti-inflammatory properties, while producing proteins capable of cartilage regeneration.[17,39-41] CTPs are commonly isolated from the bone marrow, adipose tissue, muscle tissue, synovial tissue, amniotic fluid, and placenta tissue.[38] Recently, adipose-derived stromal cells (AD-MSCs) have become increasingly popular because of ease of accessibility and harvest,[42,43] as they possess $\leq$300-fold more stem cells per volume than BMAC.[44,45] It is imperative to note that the benefits of these agents may have little to do with progenitor cell differentiation but rather are likely due to a paracrine influence in the environment into which they are placed.

## Pathology of the Articular Cartilage

Focal defects to the articular cartilage within the knee are common, present in $\leq$60% of patients undergoing knee arthroscopy.[18,46] Focal chondral lesions result in alterations in loading due to decreased contact area, placing greater stress on the surrounding cartilage, increasing the potential for degeneration and the development of early-onset OA.[18,47,48] Early intervention for the treatment of focal chondral defects, with or without surgical intervention, is recommended to improve joint function, restore contact kinematics, and minimize the risk for further injury and arthritic development (Table 1).[18]

### Hyaluronic Acid

The role of HA for the treatment of focal chondral defects has primarily been described in combination with surgical procedures.[5,38,49] The combination of an

**Table 1.** Regenerative therapy for articular cartilage pathology—clinical studies summary

| Study | LOE | Year of Publication | Type of Intervention | Adjunctive to Surgery (Y/N) | Sample Size | | Intervention Details | | Follow-Up (mo) | Favorable Outcome (Y/N) | Results Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Test Group | Control Group | Test Group | Control Group | | | |
| Gobbi et al. [6] | II | 2016 | HA scaffold + BMAC | N | 27 | 50 | HA scaffold + BMAC | Mfx | 60 | Y | At 5 y, significantly better Tegner, IKDC objective, and KOOS scores in the HA scaffold + BMAC group |
| Danieli et al [50] | II | 2020 | LP-PRP | Y | 33 | 31 | LP-PRP + chondroplasty/ debridement | Chondroplasty/ debridement | 24 | Y | Significant improvement in IKDC, KOOS, and Tegner scores in the PRP group |
| Lee et al. [51] | IV | 2013 | PRP + Mfx | Y | 24 | 25 | PRP + Mfx | Mfx | 24 | Y | At 2 y, significantly better VAS, IKDC scores, and tissue quality on postarthroscopic findings in the PRP + Mfx group |
| Papali et al. [52] | IV | 2016 | PRP + Mfx (intraop) PRP + Mfx | Y | 31 | 17 | PRP + Mfx (postop) | Mfx | 60 | Y | Significant improvement in IKDC, VAS pain, and improved postoperative appearance of cartilage on MRI in PRP + Mfx group |
| Oladeji et al. [54] | III | 2017 | BMA + OCA graft | Y | 29 | 17 | BMA + OCA graft | OCA graft alone | 6 | Y | Significantly improved OCA graft incorporation at 6 mo with reduced sclerosis in BMA group |
| Jo et al. [55] | III | 2017 | ASC | N | 12 | 6 | High-dose ASC (n = 12) | Low-dose ASC (n = 3), medium-dose ASC (n = 3) | 24 | Y | All groups had improvement in PROs with increase in cartilage and decrease in defect size at 6 mo; significant improvement in PROs with high-dose ASC |
| Koh et al. [56] | I | 2016 | AD MSC | | 40 | 40 | AD MSC | MFx | 27 | Y | Clinical benefit for patients receiving adipose-derived MSC at 27 mo |
| Hashimoto et al [57] | II | 2019 | BM-MSC | Y | 7 | 4 | BM-MSC + MFx | MFx alone | 12 | N | No clinical benefit for patients receiving BM-MSC + MFx at 48 wk |
| Brittberg et al 2018 [58] | I | 2018 | MACI | Y | | | MACI | MFx | 60 | Y | Clinical benefit for patients treated with ACI |
| Fossum et al [59] | I | 2019 | ACI-C | Y | 21 | 20 | ACI-C | AMIC | 24 | N | No difference between groups in KOOS at 24 mo |
| Volz et al [60] | II | 2017 | AMIC | Y | 30 | 9 | AMIC | MFx | 60 | Y | Clinical improvement in modified Cincinnati score at 5 y with AMIC treatment |
| Kon et al 2009 [61] | I | 2009 | ACI-C | Y | | | ACI-C | MFx | 60 | Y | Improved IKDC and Tegner for patients receiving ACI at 5 y compared with MFx |
| Niemeyer et al [62] | II | 2019 | Scaffold-free ACI | Y | 52 | 50 | Scaffold-free ACI | MFx | 24 | N | No benefit in overall KOOS for patients receiving ACI |

ACI, autologous chondrocyte implantation; ACI-C; autologous chondrocyte implantation-collagen; AD, adipose-derived; AMIC, autologous matrix induced collagen; ASC, adipose stem cell; BM, bone marrow; BMA, bone marrow aspirate; BMAC, bone marrow aspirate concentrate; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; LOE, level of evidence; LP, leukocyte-poor; MACI, matrix induced chondrocyte implantation; Mfx, microfracture; MRI, magnetic resonance imaging; MSC, mesenchymal stromal cell; OCA, osteochondral allograft; PRO, patient-reported outcome; PRP, platelet-rich plasma; VAS, visual analog score.

HA scaffold + BMAC injection with arthroscopic debridement for focal cartilage lesions without microfracture has been shown to yield superior clinical outcomes at 5-year follow-up compared with isolated microfracture.[6] Hyaline-like cartilage has been reported to develop within defects, resulting in improved pain and functional outcome scores when HA is used with BMAC + osteochondral grafting in patients with high-grade cartilage lesions.[5,49]

### Platelet-Rich Plasma

Isolated use of PRP for focal chondral defects has been infrequently reported. When used as an adjunct during surgery, PRP has demonstrated promising results. In patients with International Cartilage Repair Society (ICRS) grade III knee chondral injuries treated by chondroplasty and PRP, Danieli et al.[50] reported significant improvements in outcomes out to 2 years compared with chondroplasty alone. Lee et al.[51] reported improved clinical outcomes and tissue quality for patients undergoing microfracture + PRP injection versus microfracture alone for focal chondral lesions $<4$ cm$^2$ with minimum 2-year follow-up. Papalia et al.[52] reported that patients treated with microfracture + PRP injected either intraoperatively or postoperatively reported greater improvement in clinical outcome scores and magnetic resonance imaging (MRI) appearance of cartilage compared with microfracture alone.

### Bone Marrow Aspirate Concentrate

Injection of BMAC + HA scaffold with concurrent arthroscopic debridement has been reported to result in superior results at 5-year follow-up compared with microfracture alone for cartilage lesions measuring 0.5 to 2.2 cm.[6] Improved cartilage maturation and fill has been reported in patients with grade 3 or 4 chondral defects undergoing treatment with a scaffold supplemented with BMAC compared with patients treated with scaffold alone.[34] When evaluating the efficacy of BMAC in an HA scaffold compared with microfracture alone for full-thickness chondral defects, Whyte et al.[53] reported significant improvement in clinical outcomes in 50 patients at 2-year follow-up. Moreover, 100% of patients classified their functionality as "normal" or "nearly normal" compared with only 64% of patients undergoing microfracture. A follow-up study reported maintained improvements in clinical outcomes and functionality at 5-year follow up.[6] Oladeji et al.[54] examined outcomes for osteochondral grafts saturated in BMAC for 2 minutes before transplantation compared with grafts without BMAC. Graft incorporation was found to be significantly increased in the BMAC group at 6 months, with significantly less sclerosis appreciated at 6-week and 3-month follow-ups.

### Mesenchymal Stromal Cells

A randomized controlled trial (RCT) found that isolated intraarticular injection of AD-MSCs for focal defects led to a significant improvement in clinical outcomes at 6-month follow-up, while significantly decreasing defect size and increasing the amount of cartilage in the joint.[55] When it was used as an adjunct during surgical intervention, Koh et al.[56] found that in 80 patients with focal defects $\geq 3$ cm$^2$ treated with microfracture + AD-MSCs injection had improved MRI appearance of cartilage lesions at 2-year follow-up compared with patients undergoing microfracture alone. However, no difference in outcome scores or tissue quality during second-look arthroscopy were appreciated between groups. In contrast, an RCT comparing bone marrow–derived mesenchymal stem cells (BMSCs) with microfracture to microfracture alone reported no clinical benefit in patients receiving BMSCs with microfracture at 48 weeks.[57]

### Matrix Cell–Based Therapy

The use of matrix cell–based cell therapy was reported by Brittberg et al.[58] to result in superior outcomes at 5-year follow-up compared with patients undergoing microfracture alone for symptomatic cartilage knee defects $\geq 3$ cm$^2$. Moreover, Fossum et al.[59] reported significant improvements in clinical outcomes at 2 years in patients with symptomatic chondral or osteochondral defects ($>2$ cm$^2$) of the distal femur or patella treated with autologous matrix-induced chondrogenesis (AMIC®) or collagen-covered autologous chondrocyte implantation (ACI-C). Volz et al.[60] reported significant functional improvement at $\leq 5$ years in patients with isolated cartilage defects (2 to 3 cm$^2$) of the knee located on the medial or lateral femoral condyle, trochlea, or patella treated with AMIC using a type I/III collagen membrane compared with microfracture alone. In addition, Kon et al.[61] reported that patients undergoing ACI-C for grade III to IV chondral lesions (1 to 5 cm$^2$) of the femoral condyles or trochlea reported improved International Knee Documentation Committee (IKDC) and Tegner scores at 5 years compared with patients treated with microfracture alone. Meanwhile, treatment for chondral defects (1 to 4 cm$^2$) with ACI using spheroids consisting of chondrocytes and their own extracellular matrix in a physiological sodium-chloride solution was reported by Niemeyer et al.[62] to result in improved functional outcomes and morphological repair in patients at $\leq 24$ months.

## Pathology of Osteoarthritis

### Brief Overview

Knee OA is the most common joint disorder in the United States.[19-21] Globally, knee OA was ranked as the

11th highest contributor to global disability.[63] As a progressive disease involving multiple metabolic, genetic, and biomechanical variables, no curative therapies currently exist for the treatment of knee OA.[36,64,65] The use of various orthobiologics alone and as an adjunct during surgical treatment for knee OA has gained increasing popularity to help improve function and decrease pain in patients with symptomatic knee OA (Table 2).

### Hyaluronic Acid

The use of HA injections for the treatment of knee OA remains controversial despite its continued use for patients with moderate OA.[66] The American Academy of Orthopaedic Surgeons reported in their 2013 clinical practice guidelines that HA use for the management of OA was not supported.[67] A meta-analysis analyzing 89 randomized trials involving 12,667 patients comparing HA to sham injections versus no intervention found that HA produced a small and clinically irrelevant benefit, leading the authors to discourage HA.[68] Meanwhile, a systematic review[69] found that compared with nonsteroidal anti-inflammatory drugs, corticosteroids (CSI), PRP, and placebo, HA possessed the highest level of evidence supporting its use for early OA, with improvements in function and pain for $\leq$26 weeks. Moreover, the Osteoarthritis Research Society International group concluded that HA was preferable to CSI because of its beneficial effects on pain at and beyond 12 weeks.[70]

### Platelet-Rich Plasma

Outcomes following the use of PRP for the treatment of knee OA remain varied and controversial.[71] An RCT reported that 3 weekly injections of PRP resulted in significant improvement in total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) of 78% at 12 months versus only a 7% improvement with saline injections.[71] An RCT comparing 41 patients with moderate knee OA treated with a single PRP injection reported significantly greater pain relief, ability to perform activities of daily living, and quality of life versus CSI.[72] An RCT of 87 knees randomized to receive leukocyte-poor (LP)-PRP, normal saline, or HA reported that only the LP-PRP group maintained improvement in WOMAC and IKDC scores at 12-month follow-up.[25] Moreover, patients treated with LP-PRP were the only group to surpass the minimum clinically important difference in WOMAC scores. Meanwhile, Cole et al.[7] analyzed 99 patients randomized to 3 weekly injections of LP-PRP versus HA and reported significant improvement in visual analog score (VAS) and IKDC scores at 24- and 52-week follow-up in the LP-PRP group.

In contrast, a clinical trial of 192 patients with Kellgren-Lawrence (KL) knee OA grade <3 randomized to receive either 3 weekly injections of leukocyte-rich (LR)-PRP or HA injections reported that despite significant improvements in patient-reported outcomes (PROs) in both groups, no significant differences were noted between groups.[73] di Martino et al.[74] found in their RCT evaluating 5-year outcomes in 192 patients receiving either LR-PRP or HA injection that no significant differences in outcomes were observed at any time point between groups. When examining outcomes following LP-PRP injection versus CSI + HA in 120 patients, Huang et al.[75] reported no significant differences at 3-month follow-up. Moreover, the LP-PRP group had significantly lower WOMAC scores at 6, 9, and 12 months after injection, with significantly lower VAS scores at 12 months.

### Bone Marrow Aspirate Concentrate

Limited clinical data have been reported evaluating the efficacy of BMAC for the treatment of knee OA. Chahla et al.[76] reported in their systematic review that despite a number of studies reporting good to excellent outcomes with improvements in pain and function and few adverse side effects, no RCTs were included, with substantial heterogeneity existing between studies.[77,78] Recently, an RCT evaluating the efficacy of BMAC in 25 patients with bilateral knee OA (KL grade 1 to 3), with each joint randomized to receive either BMAC or saline injection, reported significant improvements in International Intermittent and Constant Osteoarthritis Pain (ICOAP) and VAS scores at 1-week and 3- and 6-month follow-up for both groups,[77] with no significant difference noted between groups at any time point. A follow-up study at 12 months found significant improvements in pain for both groups, with no significant differences in outcomes between groups.[79]

### Mesenchymal Stromal Cells

In an RCT of 30 patents with knee OA (KL grade 2 to 4), Lamo-Espinosa et al.[80] reported that patients receiving injection of high-dose bone marrow–derived mesenchymal stromal cells (BM-MSCs) and HA had significant improvement in VAS and WOMAC at 6- and 12-month follow-up compared with patients treated with HA alone. Similarly Emadedin et al.[81] reported that patients with knee OA (KL grade 2 to 4) treated with intra-articular implantation of BM-MSCs had significant improvement in painless walking distance and WOMAC scores compared with placebo injection at 6-month follow-up.

Lu et al.[82] compared intra-articular injections of adipose-derived mesenchymal stem cells (AMSCs) digested in 0.075% type I collagenase solution, isolated via centrifugation and subsequently culture expanded via 3 passages, to HA in 53 patients with knee OA (KL grade 1 to 3) randomized to 1 of the 2 study arms. Patients undergoing AMSC injections reported

**Table 2.** Regenerative therapy for osteoarthritis—clinical studies summary

| Study | LOE | Year of Publication | Type of Intervention | Adjunctive to Surgery (Y/N) | Sample Size | | Intervention Details | | Follow-Up (mo) | Favorable Outcome (Y/N) | Results Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Test Group | Control Group | Test Group | Control Group | | | |
| Smith et al[71] | I | 2016 | LP-PRP | N | 15 | 15 | PRP | CSI | 12 | Y | Significant improvement of 78% in total WOMAC at 12 mo with single injection of PRP |
| Forogh et al.[72] | I | 2015 | PRP | N | 24 | 24 | PRP (single injection) | CSI (single injection) | 6 | Y | Significantly greater pain relief, ability to perform activities of daily living, and quality of life with single injection of PRP |
| Lin et al.[25] | I | 2019 | LP-PRP | N | 60 | 27 | LP-PRP (31); HA (29) | NS (27) | 12 | Y | Significantly greater and maintained improvement in WOMAC and IKDC scores with LP-PRP injection |
| Cole et al.[7] | I | 2016 | LP-PRP | N | 49 | 50 | LP-PRP | HA | 12 | Y | Significant improvement in VAS and IKDC scores at 24- and 52-wk follow-up with LP-PRP |
| Filardo et al.[73] | I | 2015 | LP-PRP | N | 94 | 89 | LP-PRP | HA | 12 | N | No significant difference between 3 weekly injections of LR-PRP and single HA injections despite significant improvements in PROs |
| di Martino et al.[74] | I | 2019 | LP-PRP | N | 85 | 82 | LP-PRP | HA | 60 | N | No significant differences in outcomes between LR-PRP and HA at any time point |
| Huang et al.[75] | I | 2019 | LP-PRP | N | 80 | 40 | LP-PRP (40); HA (40) | CSI (40) | 12 | N | Single injection LP-PRP led to significantly lower WOMAC scores at 6, 9, and 12 mo compared with HA + CSI |
| Shapiro et al.[79] | I | 2018 | BMAC | N | 25 | 25 | BMAC | Saline | 12 | N | No significant differences in ICOAP and VAS scores at 12 mo between BMAC and saline injection |
| Lamo-Espinoza et al[80] | I | 2016 | BM MSC + HA | N | 20 | 10 | BM MSC + HA | HA | 12 | Y | Significant improvement in VAS and WOMAC at 6-and 12-mo follow-up with injection of AMSCs |
| Emadedin et al[81] | I | 2018 | BM MSC + HA | N | 22 | 25 | BM MSC + HA | HA | 6 | y | Significant improvement in painless walking distance and WOMAC in patients receiving BM MSC, no significant difference in VAS |
| Lu et al.[82] | I | 2019 | AMSC | N | 26 | 26 | BMAC | HA | 12 | Y | Significant improvement in VAS and SF-12 at 6-and 12-mo follow-up with injection of AMSCs |
| Lee et al.[83] | I | 2019 | ASC | N | 12 | 12 | ASC | Saline | 6 | N | Significant improvement in WOMAC score at 6-mo follow-up with both ASC and saline injection; no significant difference between groups |
| Freitag et al.[84] | I | 2018 | ASC | N | 20 | 10 | ASC × 1 injection (10); ASC × 2 injections 10) | No injections (10) | 12 | Y | Significant improvements in VAS and WOMAC score in patients receiving BM MSC at 6 and 12 mo |

AMSC, adipose mesenchymal stem cell; ASC, adipose stem cell; BM, bone marrow; BMAC, bone marrow aspirate concentrate; CSI, corticosteroids; HA, hyaluronic acid; ICOAP, International Intermittent and Constant Osteoarthritis Pain; IKDC, International Knee Documentation Committee; LOE, level of evidence; LP, leukocyte-poor; MSC, mesenchymal stromal cell; NS, normal saline; PRO, patient-reported outcome; PRP, platelet-rich plasma; SF-12, 12-Item Short Form Health Survey; VAS, visual analog score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

significant improvement in VAS and 12-Item Short Form Health Survey (SF-12) at 6- and 12-month follow-up. A significant increase in the volume change of cartilage based on MRI was noted in the ASC group at 12-month follow-up. Clinical outcomes in 24 patients undergoing ASC versus saline injections reported a 55% improvement in WOMAC score at 6-month follow-up compared with baseline values ($P < .001$); however, no significant differences in improvement were observed between groups.[83] When examining the number of ASC injections, Freitag et al.[84] analyzed 30 patients with knee OA (KL grade 2 to 3) randomized to receive 1 or 2 injections (at baseline and at 6 months) versus a control group treated without injection. Patients receiving 1 or 2 ASC injections had significant improvements in pain and WOMAC score compared with control patients at 12-month follow-up. Moreover, the minimum clinically important difference threshold was surpassed in 84.1% and 87.1% of the 1- and 2-injection groups, respectively. A systematic review of 16 studies analyzing the use of AD-MSCs for the treatment of knee OA reported improvements in clinical outcomes compared with baseline measures.[85] However, adverse reactions, consisting primarily of pain and swelling at the injection site, were reported in 5% of cases.

### Vitamin D

An investigation by Sanghi et al.[86] reported on 107 patients with knee OA and vitamin D insufficiency, randomized to treatment with 60,000 IU oral vitamin D daily for 10 days, followed by 60,000 IU once a month, versus placebo. At 12-month follow-up, significant biochemical changes in serum total vitamin $D_3$ and alkaline phosphatases were observed in patients treated with vitamin D supplementation, with a small but statistically significant improvement in VAS and WOMAC scores compared with patients receiving placebo.

It remains unknown whether vitamin D supplementation delays the progression of OA or produces a clinically significant effect on pain and function.[87] McAlindon et al.[88] observed no improvement in knee function or reduction of cartilage volume loss in patients receiving 2000 IU vitamin D daily with dose escalation to elevate serum levels to >36 ng/ml. Meanwhile, Arden et al.[89] reported no significant improvement in pain, function, or delay of joint space narrowing in patients administered 800 IU of vitamin D daily. Similarly, Jin et al.[90] observed no improvement in WOMAC knee pain or reduction of cartilage volume loss in patients consuming 50,000 IU vitamin D monthly (Table 3).

**Table 3.** Dietary supplements for Osteoarthritis—Clinical Studies Summary

| Study | LOE | Year of Publication | Type of Intervention | Adjunctive to Surgery (Y/N) | Sample Size | | Intervention Details | | Follow-Up (mo) | Favorable Outcome (Y/N) | Results Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Test Group | Control Group | Test Group | Control Group | | | |
| Sanghi et al[86] | I | 2013 | Vitamin D | N | 51 | 52 | Cholecalciferol 60,000 IU daily for 10 d followed by 60,000 IU monthly for 12 mo | Placebo | 12 | Y | Small improvement in VAS and WOMAC |
| McAlindon et al[88] | I | 2013 | Vitamin D | N | 73 | 73 | Cholecalciferol 2000 IU daily with dose escalation to elevate serum levels to >36 ng/ml | Placebo | 24 | N | No improvement in knee function or reduction of cartilage volume loss in patients with vitamin D supplementation |
| Arden[89] | I | 2016 | Vitamin D | N | 188 | 198 | Cholecalciferol 800 IU daily | Placebo | 36 | N | No significant improvement in pain or function or delay of joint space narrowing in patients with vitamin D supplementation |
| Jin[90] | I | 2016 | Vitamin D | N | 209 | 204 | Cholecalciferol 5000 IU monthly | Placebo | 24 | N | No improvement in WOMAC knee pain nor reduction of cartilage volume loss in patients with vitamin D supplementation |

LOE, level of evidence; VAS, visual analog score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

## Pathology of the Meniscus

### Brief overview

Injuries to the meniscus represent the most common pathology treated by orthopaedic surgeons, with ≤61%

of patients possessing pathology on imaging.[91,92] Meniscal injuries are associated with decreased function and adverse changes in knee contact kinematics, increasing the risk for chondral injury and degeneration.[93,94] Partial and total meniscectomy have been shown to result in higher contact pressures within the knee,[95-97] leading to increased emphasis on meniscal preservation through meniscal repair.[93,94,98,99] However, relatively high repair failure rates have been reported,[100,101] attributed to the unfavorable healing environment within the knee (Table 4).[102]

### Fibrin Clot

An early investigation[103] examined 5 patients with complete radial tears of the lateral meniscus treated with repair and a fibrin clot. Second-look arthroscopy found that all repairs demonstrated healing at the periphery, with all patients returning to their prior level of activity. Ra et al.[10] reported on 12 patients with complete radial tears of the meniscus undergoing arthroscopic inside-out repair with fibrin clots. Improvements in Lysholm and IKDC subjective knee scores were reported at a mean of 30 ± 4 months, and 11 of 12 cases demonstrated complete healing based on MRI, along with complete healing in 6 of 7 patients undergoing second-look arthroscopy. Kamimura et al.[104] reported that in 10 patients undergoing repair, significant improvements were reported based on mean Lysholm and IKDC scores at mean follow up of 40.8 ± 5.4 months, and second-look arthroscopy demonstrated complete healing in 70% of patients.

### Platelet-Rich Plasma

Blanke et al.[9] reported that in 10 recreational athletes with intrasubstance meniscal lesions treated using percutaneous intrameniscal injections of PRP, significant improvement in average pain rating scale score were appreciated at 6-month follow-up.

Augmentation of meniscal repair with PRP has been more widely reported.[105] A systematic review of 6 studies including 309 patients undergoing meniscal repair + PRP augmentation versus 445 patients treated with repair alone reported repair failures in 17% of patients with PRP versus 22.1% of patients without PRP at a mean follow-up of 32.8 months.[105] Kaminski et al.[106] reported significant improvements in patients receiving PRP + repair versus repairs alone. Meniscal healing, evaluated on second-look arthroscopy or MRI, was present in 85% of repairs augmented with PRP versus 47% in the non-PRP group ($P = .048$).[90] The systematic review conducted by Sochacki et al.[107] consisting of 5 articles analyzing 110 patients treated with PRP + meniscal repair versus 164 with repair alone reported that repairs augmented with PPR had a significantly lower failure rate (range 4.4% to 26.7%) compared with repairs without PRP (range 13.3% to 50%; $P = .03$). The conflicting results in healing rates and PROs can be attributed largely to the differences in PRP formulation, with variable concentrations of platelets, leukocytes, and growth factors.[105]

### Bone Marrow Aspirate Concentrate

A basic science investigation[8] using a rabbit model with avascular meniscal lesions reported that repairs augmented with BMAC led to superior macroscopic and histologic healing compared with specimens treated with repair + PRP or repair alone at 6 and 12 weeks. Use of BMAC and collagen wrapping for repaired meniscal lesions in 50 consecutive patients led significant improvement in clinical outcomes at 2-year follow-up, and postoperative MRI demonstrated no evidence of meniscal re-tearing in 76% of menisci.[108]

### Mesenchymal Stromal Cells

A randomized, double-blind controlled study[11] evaluated 55 patients undergoing partial meniscectomy 7 to 10 days after surgery with injection of either 50 million (group A) or 150 million (group B) bone-marrow–derived allogeneic MSCs suspended in a sodium hyaluronate solution compared with patients undergoing injection with the suspension alone (group C).[11] Significant meniscal volume gain on MRI was reported in 24% of patients in group A, 6% of patients in group B, and no patients in group C. A prospective case study reported on a series of 5 patients with bone marrow–derived MSCs placed onto a collagen scaffold arthroscopically implanted before meniscal repair using sutures.[109] At 24-month follow-up, clinical improvements were reported in Tegner, Lysholm, and IKDC scores; however, 2 patients required subsequent partial meniscectomy. A systematic review of 4 studies evaluating the use of MSCs for meniscal regeneration[110] reported that despite improvements in VAS score, marked differences in stem cell harvest method (bone marrow autograft, n = 2; bone marrow allograft, n = 1; fat-derived via liposuction, n = 1) and route of administration (percutaneous injection, n = 3; collagen scaffold, n = 1) were recorded.[110]

## Tendon Pathology

### Brief Overview

Disease and injury to tendons account for 30% to 50% of all musculoskeletal injuries.[111,112] Tendon pathology ranges from acute tears to chronic degenerative overuse.[113,114] Treatment is largely determined by the specific tendons involved, location (intratendinous versus myotendinous), and timing (acute versus chronic).[115] In the setting of acute tears, treatment is aimed at promoting cellular proliferation and healing, whereas chronic tendinopathy is managed by targeting inflammatory

**Table 4.** Regenerative Therapy for Meniscus Pathology—Clinical Studies Summary

| Study | LOE | Year of Publication | Type of Intervention | Adjunctive to Surgery (Y/N) | Sample Size | Intervention Details | | Follow-Up (mo) | | Favorable Outcome (Y/N) | Results Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Test Group | Control Group | Test Group | Control Group | | |
| van Trommel et al.[103] | IV | 1998 | Fibrin clot with meniscus repair | Y | 5 | n/a | Fibrin clot | n/a | Only 3/5 followed up (average 71 mo) | Y | 5 patients treated with fibrin clot and meniscus repair demonstrated healing on second-look arthroscopy, with all patients returning to prior level of activity |
| Ra et al.[10] | Iv | 2013 | Fibrin clot with meniscus repair | Y | 12 | n/a | Fibrin clot | n/a | Average 30-mo follow-up | Y | 12 patients treated with fibrin clot and meniscus repair demonstrated improved Lysholm and IKDC scores and healing on MRI |
| Kamimurai et al.[104] | IV | 2014 | Fibrin clot with meniscus repair | Y | 10 | n/a | Fibrin clot | n/a | Average 41-mo follow-up | Y | 10 patients treated with fibrin clot and meniscus repair report improved Lysholm and IKDC scores and healing on MRI |
| Blanke et al[9] | iV | 2015 | PRP | N | 10 | n/a | PRP | n/a | 6 | Y | Significant improvement in average pain rating scale score at 6-mo follow-up |
| Kaminski et al.[106] | I | 2014 | PRP + Meniscal repair | Y | 19 | 18 | PRP | Saline | 42 | Y | PRP injection at the time of meniscal repair led to significant meniscal healing in on second-look arthroscopy and MRI |
| Piontek et al.[108] | IV | 2016 | BMAC + collagen wrapping + meniscal repair | Y | 53 | n/a | BMAC + Collagen wrapping | n/a | 24 | Y | Significant improved in clinical outcomes with evidence of decrease rate of meniscal re-tearing on MRI |

(continued)

**Table 4.** Continued

| Study | LOE | Year of Publication | Type of Intervention | Adjunctive to Surgery (Y/N) | Sample Size | Intervention Details | | Follow-Up (mo) | | Favorable Outcome (Y/N) | Results Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Test Group | Control Group | Test Group | Control Group | | |
| Vangsness et al.[11] | I | 2014 | BM-derived allogeneic MSC | Y | 36 | 19 | MSC 50x10-6 (18) MSC 150x10-6 (18) | Sodium hyaluronate (19) | 12 | Y | Significantly increased meniscal volume (defined a priori as a 15% threshold) determined by quantitative MRI in MSC group 12 mo after meniscectomy |

BMAC, bone marrow aspirate concentrate; IKDC, International Knee Documentation Committee; LOE, level of evidence; MRI, magnetic resonance imaging; MSC, mesenchymal stromal cell; n/a, not applicable; PRP, platelet-rich plasma.

mediators and inhibiting matrix-degrading proteinases to improve healing (Table 5).[115]

### Hyaluronic Acid

HA has been shown to increase tenocyte viability and type collagen I production and deposition and reduce the surface friction of tendons.[116-120] A prospective study investigating outcomes after a single injection of HA to the patellar tendon with 1-week follow-up reported significant improvement in VAS pain score.[14] Similarly, 50 patients with patellar tendinopathy (Blazina grade 2 to 3) reported good to excellent outcomes at a mean follow-up of 25.7 months after an average of 2 HA injections.[121]

### Platelet-Rich Plasma

An RCT comparing LR-PRP to dry needling for patellar tendinopathy reported improvement in both groups, with significant improvement in Victorian Institute of Sports Assessment—Pain (VISA-P) score with PRP at 12 weeks ($P = .02$).[12] Another RCT of 46 patients with patellar tendinopathy comparing PRP injections versus focused extracorporeal shockwave therapy in athletes reported no significant differences between groups at 2-month follow-up.[122] However, significant improvement in VISA-P and VAS scores at 6- and 12-month follow-up were recorded in the PRP group. Several other studies, albeit of lower evidence, have supported the use of PRP for knee tendinopathies.[123,124] Meanwhile, a RCT by Scott et al.[125] compared LR-PRP versus normal saline injections in athletes with patellar tendinopathy for >6 months. No significant differences in VISA-P, pain, or global rating of change were reported between treatment groups. There remains a paucity of evidence regarding outcomes when PRP is used as an adjuvant for patellar tendon surgery, although patellar tendon tenotomy with subsequent repair and PRP injection for recalcitrant tendinopathy has been described.[126]

### Bone Marrow Aspirate Concentrate

A retrospective case series[13] reporting on 8 patients with refractory patellar tendinopathy treated with BMAC reported statistically significant improvement in most clinical scores at yearly follow-up, starting at 12 months. At final follow-up (range 24 to 60 months), 7 of 8 patients reported they would undergo the procedure again.

### Mesenchymal Stromal Cells

A preclinical study using a rabbit model with a patellar tendon defect in the central portion of the patellar tendon examined the use of tendon-derived stem cells (TDSCs) + fibrin compared with fibrin alone.[127] Significantly higher ultimate stress and Young's modulus was reported in the TDSC group, concluding that the use of TDSCs promoted earlier and improved tendon repair. A double-blind study of 60 knees in 46 patients with refractory patellar tendinopathy reported significantly

**Table 5.** Regenerative therapy for tendon pathology—clinical studies summary

| Study | LOE | Year of Publication | Type of Intervention | Adjunctive to Surgery (Y/N) | Sample Size | | Intervention Details | | Follow-Up (mo) | Favorable Outcome (Y/N) | Results Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Test Group | Control Group | Test Group | Control Group | | | |
| Muneta et al.[121] | IV | 2012 | HA | N | 50 | none | HA | none | 6-88 | Y | 54% return to previous athletic activities with little difficulty and 40% return to previous sporting activities with some degree of limitation |
| Dragoo et al.[12] | I | 2014 | LR-PRP with dry needling | N | 10 | 12 | LR- PRP | Dry needling | 3 | Y | Significant improvement in VISA-P score with PRP at 12 wk |
| Vetrano et al[122] | I | 2013 | PRP | N | 23 | 23 | PRP ×2 injections | ESWT | 12 | Y | Significant better improvement of VISA-P and VAS scores at 6- and 12-mo follow-up and modified Blazina scale score at 12-mo follow-up with PRP |
| Scott et al.[125] | I | 2019 | LR-PRP | N | 36 | 19 | LR-PRP (19); LP-PRP (19) | Saline (19) | 12 | N | Single injection of LR-PRP or LP-PRP was no more effective than saline for the improvement of patellar tendinopathy symptoms |
| Pascual-Garrido et al.[13] | IV | 2012 | BM-MNC | N | 8 | None | BM-MNC | None | 60 | Y | Significant improvement in most clinical scores at yearly follow-up with use of BM-MNCs |
| Clarke et al.[128] | I | 2010 | Skin-derived tenocyte-like collagen-producing cells | N | 23 | 23 | TDSC + PRP | PRP alone | 6 | Y | Significantly higher VISA scores at 6-mo follow-up in patients receiving skin-derived tenocyte-like collagen-producing cell |

BM, bone marrow; ESWT, extracorporeal shockwave therapy; HA, hyaluronic acid; LOE, level of evidence; LP, leukocyte-poor; LR, leukocyte-rich; MNC, mononuclear cell; PRP, platelet-rich plasma; TDSC, tendon-derived stem cell; VAS, visual analog score; VISA-P, Victorian Institute of Sports Assessment — Pain.

higher VISA scores at 6-month follow-up in patients receiving skin-derived tenocyte-like collagen-producing cells versus autologous plasma, with histopathology showing normal tendon structure.[128]

## Pathology of the Ligaments

### Brief Overview

Ligament injuries account for approximately 40% of all knee injuries.[129,130] Injuries often result in recurrent instability, muscle weakness, and reduced functional performance, with long-term clinical sequelae including meniscal tears, chondral lesions, and increased risk of early-onset post-traumatic OA. Injuries most commonly involve the medial collateral ligament (MCL) and anterior cruciate ligament (ACL).[131] MCL injuries are most commonly treated with early mobilization and nonoperative management,[132] whereas ACL injuries possess poor healing capacity with potential for failure after reconstruction.[133-135] Biological strategies have been proposed for both conservative treatment and augmentation during ACL reconstruction to promote graft maturation and osteoligamentous graft integration (Table 6).[136]

### Platelet-Rich Plasma

Seijas et al.[137] reported on intraligamentous administration of 4 mL PRP product (PRGF-Endoret)[138] in 19 professional soccer athletes with partial ACL tears after reconstruction, with an additional 6 mL injected into the articular space after surgery. Eighteen athletes returned to their preinjury level of play.[137] Koch et al.[139] reported improved IKDC, Lysholm, Tegner, and Cincinnati scores at a mean follow-up of 33 months after arthroscopic intraligamentous administration of autologous conditioned plasma in 42 patients with partial ACL tears using ACP injection and healing response technique.[140] Despite promising results, neither study included a control group, making assessment of PRP on outcomes difficult to interpret.

Histological evaluation of augmented grafts has shown newly formed connective tissue in 77.3% of the platelet-rich growth factor (PRGF)—assisted ACL grafts compared with 40% of nonaugmented grafts at a minimum of 6 months.[141] An RCT matched 25 patients treated with ACL reconstruction in combination with a platelet-rich plasma gel (PRPG) to a control group with reconstruction alone.[142] Complete graft homogeneity was achieved by 179 days in the PRPG group compared with 369 days in the non-PRPG group, and maturation time was reduced from 12 months to 3.6 months in the PRGF group. A recent retrospective study of 143 patients <21 years of age reported decreased ACL reinjury rates requiring revision surgery in patients with ACL reconstruction coupled with PRP and a porous collagen carrier, with 132 of 143 patients returning to preinjury level.[143]

### Bone Marrow Aspirate Concentrate

A case series reported on 10 patients with partial ACL tears treated with fluoroscopically guided intraligamentous injection of autologous BMAC + PRP.[144] Seven of the 10 patients showed improved ACL integrity based on postoperative MRI; improvements in mean VAS and Lower Extremity Functional Scale were also reported.

### Mesenchymal Stromal Cells

Kanaya et al.[145] compared ACL healing using MSCs with phosphate-buffered solution versus phosphate-buffered solution alone in rats with partially torn ACL. The MSC group showed improved ligament healing, histologic features, and femur-ACL-tibia complex load-to-failure compared with controls. Recently, Alentorn-Geli et al.[146] reported on clinical outcomes of 20 soccer athletes undergoing ACL reconstruction using bone-to-bone autograft augmented with adipose tissue and other progenitor cells, collectively termed adipose-derived regenerative stem cells. No significant differences were appreciated between the augmented group and a matched cohort ($P > .05$) at 12-month follow-up.

## Prospects for the Future

Future investigations examining currently administered orthobiologics for the treatment of knee injuries require increasing focus on the standardization of solution preparations. Namely, the inconsistent results reported after orthobiologics use may be attributed to the heterogeneity of final HA, PRP, BMAC, and MSC preparations and injection regimens, largely limiting the ability to reliably and meaningfully compare outcomes between studies to determine the true efficacy and safety profiles for each treatment. As such, minimizing variability in processing and formulations is essential to advance the field of orthobiologics for orthoregeneration in patients with knee injuries. Meanwhile, further investigations evaluating the use of matrix-based cell therapies and vitamin supplementation are warranted to better understand their efficacy for the treatment of musculoskeletal disorders affecting the knee.

### Conclusion

There remains increasing interest and tremendous potential for the use of orthobiologics for the treatment of various knee injuries and pathologies. Despite a number of available studies, there remain conflicting outcomes and no consensus regarding the optimal treatment for patients sustaining injuries to the cartilage, meniscus, tendon, or ligaments of the knee. Further high-quality comparative studies are warranted

**Table 6.** Regenerative Therapy for Ligament Pathology - Clinical Studies Summary

| Study | LOE | Year of Publication | Type of Intervention | Adjunctive to Surgery (Y/N) | Sample Size | | Intervention Details | | Follow up (months) | Favorable Outcome (Y/N) | Results Summary |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Test Group | Control | Test Group | Control | | | |
| Seijas et al.[137] | IV | 2014 | PRGF | N | 19 | none | PRGF | none | 24 | Y | High return to sport rates at pre- injury level in professional football players treated with PRGF |
| Koch et al.[139] | IV | 2018 | PRP | N | 42 | none | PRP | none | 24 | Y | Significantly improved IKDC, Lysholm, Tegner, and Cincinnati scores w/ PRP |
| Sanchez et al.[141] | III | 2010 | PRGF + ACL-R | Y | 22 | 15 | PRGF | ACL-R alone | 12 | Y | Significantly improved connective tissue after PRGF augmented ACL-R on histologic evaluation |
| Radice et al[142] | III | 2010 | PRPG + ACL-R | Y | 25 | 25 | PRPG | ACL-R alone | 12 | Y | Faster complete homogeneous grafts assessed by MRI w/ PRPG + ACL-R |
| Berdis et al.[143] | IV | 2019 | PRP + ACL-R | Y | 151 | none | 151 | n/a | 25 - 94 months | Y | Significant decrease rate decreased rate of second ACL injury w/ high return to preinjury level of competition |
| Centeno et al.[144] | IV | 2015 | BMAC + PRP | N | 10 | none | 10 | none | 2.5 - 7 months | Y | Seven of 10 patients showed improved ACL integrity based on postoperative MRI and improved mean VAS and Lower Extremity Functional Scale scores |
| Alentorn-Geli et al.[146] | III | 2019 | ADRC + ACL-R | Y | 20 | 19 | ADRC | ACL-R alone | 12 | N | Improvement w/ ADRC was not statistically different from ACL reconstruction alone |

ACL-R, Anterior Cruciate Ligament Reconstruction; ADRC Adipose Derived Rich l Stem Cells; BMAC, Bone Marrow Aspirate Concentrate; IKDC, International Knee Documentation Knee; MRI, Magnetic Resonance Imaging; PRGF, Platelet Rich Growth Factors; PRP, Platelet Rich Plasma.

to analyze currently available orthobiologics therapies, while also promoting the importance of standardizing orthobiologic preparation methods and formulations.

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