Systematic Review

The Addition of Platelet-Rich Plasma to Scaffolds Used for Cartilage Repair: A Review of Human and Animal Studies

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Purpose: To review the available literature on studies focusing on platelet-rich plasma (PRP)—enhanced scaffolds for cartilage lesion repair in animals and to analyze the clinical outcomes of similar biologically augmented cartilage regeneration techniques in humans. **Methods:** We conducted a literature search and subsequent review investigating the potential of PRP to enhance articular cartilage repair using scaffolds or bioengineered implants. **Results:** Of the 14 animal model studies reviewed, 10 reported positive effects with PRP whereas only 2 showed negative overall effects. The remaining 2 studies reported no significant differences, or neutral results, with the use of PRP. With the addition of PRP, the gross appearance and histologic analysis of repair cartilage were improved or no difference was seen compared with control (11 of 12 studies that looked at this). Human studies of the knee or talar dome showed improvements in clinical assessment scores as soon as 6 months after surgery. There was great variability in the method of PRP preparation, choice of scaffold, and cell source between studies. **Conclusions:** PRP-augmented scaffolds have been shown to be beneficial in the articular cartilage repair process in animals and humans based on macroscopic, histologic, and biochemical analysis and based on clinical outcome scores, respectively. Comparison between studies is difficult because there is great variability in PRP preparation and administration. **Level of Evidence:** Level IV, systematic review of Level III and IV studies.

See commentary on page 1626

The articular surface of joints is composed of hyaline cartilage, which is unable to heal spontaneously because of its unique structure and distinctive properties.[1] This avascular tissue is composed of chondrocytes dispersed within an extracellular matrix composed of collagen and proteoglycans.[2] Structurally, mature hyaline cartilage is highly organized and is composed of superficial, middle, deep, and calcified layers, each with its own characteristics.[3] The thickness and orientation of collagen fibrils vary between zones, and the proteoglycan content increases whereas the water content decreases from the superficial to the deep zone.[2] Furthermore, the type of proteoglycan differs between the different zones. This unique composition contributes to its biomechanical role in providing a low-friction interface that also bears load and withstands shear stresses.[2,4] Unfortunately, it is this very structure that presents a considerable therapeutic challenge for repair or regeneration.[5]

The reparative response tends to be ineffectual because of the inability of chondrocytes to migrate to the site of injury and the avascular nature of cartilage.[6,7] The prognosis is worse when the defect is greater than 2 × 2 cm,[8] when the defect is in the weight-bearing portion of the articular surface, and when there is considerable bone loss.[9] The goal of cartilage repair is to integrate new, functional hyaline cartilage into the host tissue and restore the biochemical and mechanical functions of the native cartilage.[10] To this end, several interventions have been described to fill the cartilage defect. These surgical

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techniques include microfracture, allograft or autograft osteochondral transplants, and autologous chondrocyte implantation.[11-14] Although these treatment modalities may provide short-term symptomatic relief, questions still remain about the long-term sustainability because of insufficient integration with host cartilage or the lack of hyaline cartilage formation, resulting in joint degeneration and arthritis over time.[11,15-17] In fact, some reviews have shown no clinical differences between these 3 methods of cartilage repair over time.[18,19]

One of the key limitations with articular cartilage regeneration techniques has been an inability to recreate the normal morphologic structure, which is integral to its function.[20] Recent reports have shown good results with the use of matrix-assisted autologous chondrocyte implantation,[21-23] which uses a collagen membrane "scaffold," on which chondrocytes are implanted.[24] Scaffolds are 3-dimensional chondroinductive biomaterials that facilitate chondrocyte number expansion or organization (or both) and can provide mechanical support for weight bearing.[25,26] These structures may vary in composition; scaffolds made of bone- or cartilage-mimicking structures allow direct cell adherence,[27-30] whereas gel scaffolds encapsulate cells.[31-33] Studies have shown improved clinical outcomes and more durable results over time with the use of scaffolds compared with microfracture procedures.[23,34-37] Though promising, long-term trials and further knowledge regarding the effects of the degradation of these scaffolds are required. There is also a need for a standardized surgical protocol and rehabilitation, as well as clarification on whether adjunctive biological factors, such as platelet-rich plasma (PRP), would promote superior repair and healing.

Chondrocyte metabolism is guided not only by mechanical factors but also by chemical stimuli.[38] Growth factors (GFs) are thought to play a significant role in this process and have become the focus for targeted therapy to augment tissue-engineered cartilage regeneration.[39,40] PRP can easily be acquired through centrifugation of a patient's own blood, creating an autologous preparation of plasma with high concentrations of platelets, which—on activation—release an array of GFs, cytokines, and other molecules. As such, PRP has been used as a way to administer GFs to the site and to amplify the concentration of chemical mediators in the microenvironment. It is anticipated that the GFs released by the activated platelets support the proliferation of chondrocytes and extracellular matrix production.[41,42] These GFs include insulin-like growth factor (insulin-like growth factor 1), transforming growth factor β1, basic fibroblast growth factor, and platelet-derived growth factor,[41-43] which have been shown to regulate articular cartilage growth and homeostasis.[44-46] Furthermore, PRP may have an inhibitory effect on the release of interleukin 1, a cytokine

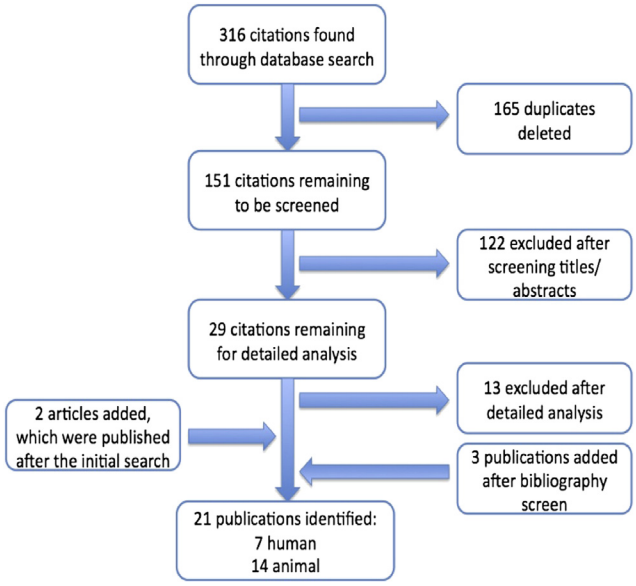

Fig 1. Search flow chart.

that impairs the healing process.[47] PRP has been shown to improve cartilage formation in vitro.[48] The addition of PRP to chondrocyte cultures was found to yield thicker cartilage with an increase in glycosaminoglycan content and enhanced mechanical properties.[48] Although the clinical efficacy of PRP remains controversial,[49,50] recent trials and reviews of intra-articular PRP injections have shown a decrease in pain and swelling in the context of osteoarthritis.[50-52]

The purposes of this study were to review the available literature on studies focusing on the healing potential of PRP-augmented scaffolds for cartilage lesion repair in animals and to analyze the clinical outcomes of similar biologically augmented cartilage regeneration techniques in humans. We hypothesized that the addition of PRP to scaffolds would enhance the gross morphology and histologic analysis of repair cartilage in animals and would improve clinical assessment scores postoperatively in humans.

Methods

Literature Search

A literature search was conducted in the following databases from inception to August 2013: Medline with daily updates, Embase Classic and Embase, Ovid Medline In-Process & Other Non-Indexed Citations, Science Citation Index Expanded, and Scopus. A search strategy was developed in an effort to answer the proposed questions as follows: "platelet" or "thrombocyte" or "platelet rich plasma" AND "scaffold" or "implant" or "tissue engineer*" AND "cartilage." There were no date or language restrictions, and all the bibliographies of included studies were manually screened for additional relevant studies. The search flow of the literature is