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BIOLOGICAL ADJUVANTS IN ORTHOPEDIC SURGERY (J DINES AND D GRANDE, SECTION EDITORS)

Biologics in Achilles tendon healing and repair: a review

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Abstract Injuries of the Achilles tendon are relatively common with potentially devastating outcomes. Healing Achilles tendons form a fibrovascular scar resulting in a tendon which may be mechanically weaker than the native tendon. The resulting strength deficit causes a high risk for reinjury and other complications. Treatments using biologics aim to restore the normal properties of the native tendon and reduce the risk of rerupture and maximize tendon function. The purpose of this review was to summarize the current findings of various therapies using biologics in an attempt to improve the prognosis of Achilles tendon ruptures and tendinopathies. A PubMed search was performed using specific search terms. The search was open for original manuscripts and review papers limited to publication within the last 10 years. From these searches, papers were included in the review if they investigated the effects of biological augmentation on Achilles tendon repair or healing. Platelet-rich plasma may assist in the healing process of Achilles tendon ruptures, while the evidence to support its use in the treatment of chronic Achilles tendinopathies remains insufficient. The use of growth factors such as hepatocyte growth factor, recombinant human platelet-derived growth factor-BB, interleukin-6, and transforming growth factor beta as well as several bone morphogenetic proteins have shown promising results for Achilles tendon repair. In vitro and preclinical studies have indicated the potential effectiveness of bone marrow aspirate as well. Stem cells also have positive effects on Achilles tendon healing, particularly during the early phases. Polyhydroxyalkanoates (PHA), decellularized tendon tissue, and porcine small intestinal submucosa (SIS) are biomaterials which have shown promising results as scaffolds used in Achilles tendon repair. The application of biological augmentation techniques in Achilles tendon repair appears promising; however, several techniques require further investigation to evaluate their clinical application.

Keywords Biologics · Platelet-rich plasma · Bone marrow aspirate · Bone morphogenetic protein · Stem cells · Growth factor · Scaffold · Achilles

Introduction

Injuries of the Achilles tendon can be devastating injuries with unpredictable outcomes. The use of biologics in optimizing clinical outcomes for Achilles tendon repairs is still in its infancy. This is evidenced by the trivial amount of improvements made to the surgical approach of Achilles tendon repair over the last 50 years [38]. It has been estimated that acute Achilles tendon rupture has an incidence of 18 per 100,000 and continues to rise [40].

Unlike bone, tendon healing does not result in tissue homologous to its prior uninjured state. Instead, a fibrovascular scar is formed which results in a tendon mechanically weaker than the native tendon [25]. The resulting strength deficit may increase risk for reinjury and other complications. Treatments of Achilles tendon injuries aim to restore the properties of the native tendon and reduce the risk of rerupture and complications. Currently, therapies utilizing biological augmentation techniques are being investigated for potential benefits in tendon healing.

The purpose of this review was to summarize the current findings of various therapies using biologics in an attempt to

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improve the prognosis of Achilles tendon ruptures and tendinopathies. The review includes the use of platelet-rich plasma (PRP), bone marrow aspirate (BMA), bone morphogenetic proteins (BMPs), stem cells, bioscaffolds, growth factors, and various combinations of these techniques.

Search strategies and criteria

A PubMed search was performed using keywords "biologics," "platelet-rich plasma," "bone marrow aspirate," "bone morphogenetic protein," "stem cells," "growth factor," and "scaffold" in combination with "Achilles." The search was open for original manuscripts and review papers limited to publication within the last 10 years. From these searches, papers were included in the review if they investigated the effects of biological augmentation on Achilles tendon repair or healing. A total of 1097 papers were identified initially and further broken down into the following categories: platelet-rich plasma (PRP), 110; bone marrow aspirate concentrate (BMAC), 4; bone morphogenic protein (BMP), 45; stem cells, 315; scaffolds, 213; growth factors, 371; and generalized reviews on biologics in tendon repair, 39.

Platelet-rich plasma

Platelet-rich plasma is defined by the American Red Cross as a sample of plasma with a twofold or more increase in platelet concentration above baseline levels or greater than 1.1×10^6 platelets/μL [22]. PRP has been shown to have a number of different growth factors. The high concentration of platelets produces granules which release growth factors including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β1 and TGF-β2 isomers), platelet-derived angiogenesis factor (PDAF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived endothelial growth factor (PDEGF), epithelial cell growth factor (ECGF), and insulin-like growth factor (IGF) [68, 17]. The resulting pool of growth factors is believed to enhance tissue recovery and may be of particular use in areas with low intrinsic healing potentials [74]. The injection of PRP can stimulate an inflammatory response and lead to new collagen deposition as demonstrated in a healthy rabbit Achilles tendon model [27]. Like other biologic therapies, the goal of PRP is to restore the injured tendon's native properties.

Some evidence supports PRPs ability to stimulate revascularization and enhance healing at the microscopic level [68]. In a rat model, PRP injections decrease collagen fiber diameters which may indicate improved healing [15]. However, the evidence for use in human chronic Achilles tendinopathy remains insufficient [60, 50, 74, 56]. In humans, the use of PRP for Achilles tendinopathy is no more beneficial than the use of placebo treatment or control [67, 16, 62] Several studies suggesting an improvement of clinical symptoms provide weak evidence with a lack of control groups [20, 23, 49, 51].

The effectiveness of PRP for the treatment of Achilles tendon ruptures should be distinguished from its effectiveness in the treatment of chronic Achilles tendinopathies [68]. The early phase of ruptured Achilles tendon healing is enhanced in rats by PRP injection after surgery as evidenced by increased early depositions of fibrillar collagen [36]. Ruptured rat Achilles tendons injected with PRP after surgery also show greater maturation of tendon callus, stronger mechanical resistance, and enhanced neovascularization which could accelerate healing and promote scar tissue with an improved histological quality [45, 4, 36]. The potential benefits in humans were demonstrated in a case study of an athlete with a partial tear who received three PRP injections and no surgical intervention. He was able to return to playing in a full basketball game just 75 days after the injury and remained without complications 18 months later [21]. An additional six athletes with ruptured Achilles tendons treated with PRP after surgery recovered their range of motion earlier and took less time to resume training as compared to athletes who underwent surgery without PRP treatment. These findings were supported by a review of 10 relevant studies conducted by Sadoghi et al. [60] showing a strong positive effect of PRP after Achilles tendon rupture treatment. All PRP treatments increased proliferation, DNA levels, and GAG levels, although lower concentrations were more effective.

Other variations of PRP have been explored as well in order to optimize the therapeutic benefits of autologous platelets. Plasma rich in growth factors (PRGF) is a type of leukocyte-poor PRP. In vitro, PRGF has a positive effect on tenocyte growth and migration [72]. A recent animal study of PRGF in surgically treated Achilles tendons resulted in histologically superior tendon repair compared to controls. Platelet-rich clot releasate (PRCR) is the acellular serum product extruded from PRP with activated platelets. In a rat Achilles tendon model, PRCR induces tenocyte differentiation while inhibiting the differentiation of adipocytes, chondrocytes, and osteocytes believed to impede on tendon healing [10].

Bone marrow aspirate

Bone marrow aspirate concentrate (BMAC) is produced by density gradient centrifugation of bone marrow usually aspirated from the iliac crest although actual stem cell numbers are less than 0.01 % or 1/100,000 nucleated cells. Its major function is to deliver mesenchymal stem cells (MSCs) to the injury site, and like PRP, BMAC is also rich in platelets and therefore growth factors [66]. In vitro studies have shown an increase in cell proliferation in Achilles tendon scaffolds seeded with bone marrow aspirate as compared to previously cultured

human bone marrow stem cells [8]. A recent preclinical study found transected rat Achilles tendons injected with bone marrow cells display greater failure load than tendons treated with MSCs or control. By 28 days after surgery, the failure load for rat Achilles tendons treated with bone marrow cells is equal to that of uninjured tendon [55]. The further investigation of the use of BMAC in a human Achilles tendon is warranted.

Bone morphogenetic proteins

Bone morphogenetic protein-12

Also known as growth and differentiation factor-7 (GDF-7), bone morphogenetic protein-12 (BMP-12) induces the formation of tendon and ligament-like tissue and is capable of promoting differentiation of stem cells into tenocytes [46]. These properties have sparked interest in its potential use for tendon healing. Majewski et al. [46] used a novel delivery method of BMP-12 by utilizing a genetically modified muscle flap on transected rat Achilles tendons. The administration of BMP-12 increased maximum failure load, tendon stiffness, organization of collagen, and size of the rupture callus as compared with controls. Combining BMP-12 with BMP-13 in a transected rat Achilles tendon model results in an increased rate of cellular infiltration, increased tissue volume, and altered levels of mRNA known to be involved in tendon repair [32].

Interestingly, the addition of BMP-12 to rat Achilles tendons does not affect growth factor expression [28]. This may explain why genetically engineered knockout mice without BMP-12 showed insignificant effects on the composition and ultrastructure of Achilles tendons. Another possible explanation could be the overcompensation of other BMP/GDF family members [48].

Bone morphogenetic protein-2

The overexpression of bone morphogenetic protein-2 (BMP-2) in the MSC line C3H10T1/2 results in differentiation to bone or cartilage. When coexpressed with the intracellular protein Smad8, BMP-2 induces new tendon formation and blocks the differentiation of MSCs into cartilage and bone tissues. Achilles tendon defects in rats treated with Smad8/BMP-2-engineered MSCs show accelerated early recovery of biomechanical properties as indicated by effective stiffness [57]. Furthermore, the use of BMP-2 in fibrin glue for the repair of a bone Achilles tendon injury in rats accelerates healing and improves the biomechanical and histological properties of the tissue [39].

Bone morphogenetic protein-7

Also known as osteogenic protein-1 (OP-1), bone morphogenetic protein-7 (BMP-7) has various effects on other members of the BMP and GDF families in vitro. Animal studies have shown the ability of BMP-7 to induce cartilage and bone formation as well as promote tendon healing and repair in rats [79]. On the contrary, in a review conducted by Aspenberg [3], BMP-7 was said to reduce the strength of tendon and predominantly support bone growth at the site of the injured tendon. The inconsistent results may be a result of BMP-7's involvement in the complex regulation of expression patterns for members of the BMP and GDF families involved in Achilles tendon repair.

Bone morphogenetic protein-14

Also known as growth and differentiation factor-5 (GDF-5), bone morphogenetic protein-14 (BMP-14) is a member of the transforming growth factor superfamily. It plays a role in tendon collagen organization at both the cellular and gene levels. However, its ability to interact with a large number of receptors causes its exact mechanism of action on cells to remain uncertain [37]. It has been shown to promote Achilles tendon healing through various delivery modalities in animal studies. BMP-14 will induce neotendon formation when injected ectopically and increase the tensile strength of the tendon when injected directly into the tendon defect [7]. When introduced into rat Achilles tendon fibroblasts, GDF-5 induced extracellular matrix (ECM) synthesis and cellular proliferation. It also increased the expression of ECM and cell adhesion-related genes [37].

Multiple delivery methods of GDF-5 in animal studies have shown promising results. Adenoviral gene transfer of GDF-5 successfully resulted in the overexpression of GDF-5 in a rat model and led to increased tensile strength without adverse immunological response [59]. The use of GDF-5-coated sutures also led to improved early tendon healing at 3 weeks after surgery [18].

Stem cells

Mesenchymal stem cells have shown promising results for the treatment of numerous Achilles tendon injuries including tendon-bone healing [33, 54]. The enhancement of repair is hypothesized to be a result of various pathways the MSCs influence along with their anti-apoptotic effect [64]. In addition, the ability to differentiate into tenocytes may be beneficial. There is evidence that the greatest effects of MSCs occur in the early phases of the healing process. In a study of rabbit Achilles tendon model, improved collagen fiber organization

was observed in tendons treated with MSCs at 3 weeks, but no significant differences were observed later in the healing process [11].

The optimal culturing and delivery methods for MSCs is important to explore when considering treatment with MSCs. Several studies have looked at MSC-coated sutures as a delivery method. This technique is meant to alleviate the concern of an "acellular zone" created when sutures are placed through tendon tissue. Yao, Korotkova, and Smith [78] were able to successfully adhere stem cells to sutures and survive the trauma of being passed through tendinous tissue. Using fluorescent microscopy, the stem cells were observed proliferating along the suture and entering the rabbit Achilles tendon while remaining metabolically active. A preclinical study comparing repair with the direct injection of MSCs and repair using sutures with MSCs showed superior results histologically for the suture group. Both groups had a significantly greater ultimate failure strength than control group [1].

One technique used to modify the effects of MSCs is to expand them under hypoxic conditions. Hypoxic MSCs show increased proliferation rate and differentiation potential. After transplantation, hypoxic MSCs display improved migration and engraftment while secreting more cytokines and growth factors than MSCs grown under normoxic conditions. When used in animal studies, ultimate failure load was significantly greater in rat Achilles tendons treated with hypoxic MSCs as compared to normoxic MSCs and controls at 2 and 4 weeks after surgery [31].

Another way to manipulate MSCs for tendon repair is to use genetically modified MSCs. The zinc finger transcription factor EGR1-producing MSCs increased the formation of tendon-like tissues in a rat Achilles tendon model [26]. Additionally, transected rat Achilles tendons treated with Smad8/BMP-2-engineered MSCs display accelerated early recovery of biomechanical properties with greater elasticity and smaller cross-sectional areas [57]. Further investigation into genetically engineered MSCs should aim to produce an optimal combination of growth factors and cytokines involved in tendon repair.

Combining the concept of platelet-rich therapies with MSC treatment may also be of interest for tendon repair. Chen et al. [10] found that platelet-rich clot releasate combined with rat tendon stem cells facilitated the proliferation and differentiation of tenocytes and actively suppressed the differentiation of cell types known to impede healing such as adipocyte, chondrocyte, and osteocyte lineages.

Alternate methods for culturing MSCs have been explored as well. For example, adipose-derived stem cells (ASCs) may be just as effective as other MSCs as measured by their multipotency and proliferative efficiency. Also, ASC may have a higher concentration of the pluripotent stem cells (2 vs. .01 %) compared to BMAC. ASCs increase the tensile strength of healing rabbit Achilles tendons while increasing collagen type I, VEGF, and fibroblast growth factor (FGF). However, transforming growth factor beta (TGF-β) is decreased by ASC treatment and the complex interactions between ASCs, growth factors, and their effects on tendon healing should be further explored [73]. Another alternative method for stem cell cultivation is to isolate circulating stem cells from the peripheral blood. When seeded on a biodegradable scaffold, MSCs collected using this method improved biomechanical properties and histological organization in healing rat Achilles tendons [14].

Despite the majority of findings suggesting stem cell therapies enhance tendon repair, Kraus et al. [41] found a lack of evidence to support the use of stem cells as a beneficial treatment in Achilles tendon repair and even suggested that it may lead to negative outcomes. At 28 days after rat Achilles tendons were ruptured, the groups receiving MSCs displayed inferior biomechanical testing as compared to the control group. These results indicate the need for a more critical evaluation of the efficacy of MSC therapies for tendon repair.

Scaffolds

Finding an effective scaffold for tendon tissue engineering has been an area of study which has received significant attention. Various materials have been examined including natural materials such as collagen or silk and manufactured materials such as synthetic polymers. In some cases, a hybrid of both natural and manufactured materials have been studied with the belief that it would promote cellular in growth while providing mechanical support for the remodeling of the tendon [76]. Aside from scaffold material, properties such as the scaffold length and whether it underwent prior mechanical stimulation can also affect the ultimate stiffness of the repaired tendon [53]. An optimal material for Achilles tendon repair would allow natural and fast bridging of tendinous defects as well as organized collagen-rich tissue with complete incorporation of the material within 8 weeks [69]. Another important feature of scaffold material may be the release of chemotactic molecules upon degradation to promote the recruitment of progenitor cells [6].

Polyhydroxyalkanoates (PHA) may serve as a good option for scaffold material in tendon repair. They are part of a family of biopolymers consisting of polyesters produced in nature by microorganisms as to store energy and carbon. Specifically, poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) (PHBHHx) is known to be compatible with many mesenchyme-derived cell types and has adaptable mechanical properties along with delayed biodegradability [76]. In an animal study conducted by Webb et al. [76], PHBHHx scaffold showed superior mechanical properties and histological results for rat Achilles tendon repair in comparison to controls.

Another option being investigated is the use of decellularized tendon tissue as a scaffold. This type of scaffold is naturally derived and it preserves the native ultrastructure, biochemical composition, and tensile strength of the tendon extracellular matrix (ECM). Furthermore, 93 % of proteoglycans and growth factors found in native tendon ECM are preserved. These scaffolds can be prepared by repetitive freeze/thaw of the tendon and nuclease treatment. In vitro, the decellularized tendon slices were able to facilitate repopulation and attachment of NIH-3T3 fibroblasts [52]. Looking at decellularized Achilles tendon-bone grafts in vivo, Farnebo et al. [19] noted the enhancement of mechanical properties and reduced immune response in a rat Achilles tendon model as compared to an untreated tendon-bone graft. Decellularized porcine tendon can also be recellularized with human tenocytes [44].

The application of acellular tissue derived from humans has been investigated for use in Achilles tendon healing as well. Acellular human dermal allograft, GraftJacket® (Wright Medical Technology, Inc, Arlington, TN, USA), showed significant improvement in mechanical strength and stiffness in repaired Achilles tendons of human cadavers [5]. Further retrospective studies indicate a desirable return-to-activity time without complications for patients treated with GraftJacket® for Achilles tendon rupture [42, 43]. However, the retrospective studies were conducted in a small number of patients and lacked reliable statistics for comparison of normal rerupture rates and return-to-activity time.

Biomaterials from other animals have also been tested as tendon scaffolds. Xenograft scaffolds in addition to suture repair have shown enhanced tendon repair in vitro compared to suture repair alone [77]. Porcine small intestinal submucosa (SIS) has been used clinically as a scaffold material for tissue reconstruction in many body systems. Preclinical animal studies have indicated that ECM from SIS is capable of being remodeled into tendon tissue [24]. SIS retains several biologically active growth factors including VEGF, TGF-β, and FGF which likely contributes to the behavior and migration of cells into the scaffold [81]. Animal studies have shown the rapid degradation of SIS after implantation with 60 % of the mass lost after 1 month and complete resorption 3 months after surgery. By 90 days, the ECM consists of dense collagenous tissue very similar to native tendon in terms of cellularity, vascularity, and organization [24]. Another advantage of SIS is its ability to recruit a population of marrow-derived cells involved in the long-term remodeling process [81]. Suckow et al. [69] showed porcine renal capsule matrix (RCM) may yield similar results to porcine SIS for use as scaffold material in Achilles tendon repair.

Scaffolds can be augmented and be potentially enhanced by the addition of exogenous factors. Adding exogenous stromal cell-derived factor-1 alpha (SDF-1 alpha) to a silk-collagen scaffold will improve the biomechanical properties of the healing tendon, increase recruitment of fibroblast-like cells, decrease accumulation of inflammatory cells, and enhance endogenous production of SDF-1 alpha and tendon ECM in a rat model. Scaffolds may also be enhanced by the addition of platelet-rich fibrin matrix (PRPFM) into the gap between the two ends of a ruptured tendon supported by a scaffold. PRPFM is produced from centrifuged autologous blood and its benefits include increased growth factors, cytokines, and hemostatic factors [61].

Scaffolds + stem cells

In order to optimize the benefits of biologic therapies, it may be advantageous to combine their applications. By seeding scaffolds with stem cells, the remodeling process can be structurally supported while increasing potential for migration and differentiation into tenocytes. Human embryonic stem cells (hESCs) alone are inadequate for optimal tendon regeneration. However, when seeded in a knitted silk-collagen scaffold, hESCs are able to differentiate into tenocytes and enhance tendon regeneration by modifying the healing environment. The environment-modifying capabilities of hESCs occur through the secretion of various cytokines, ECM, and growth factors [9].

Scaffolds must be made from a material which can adequately deliver stem cells to the healing Achilles tendon. Conventional surgical mesh is capable of delivering MSCs to the injured Achilles tendon and enhancing early functional recovery as demonstrated in a rat model [63]. When dealing with scaffolds made from biomaterial, decellularized tendinous matrices are preferable over bone or dermis matrices because stem cells are more likely to differentiate into tenocyte lineages and have osteogenic inhibition [80]. Extracellular matrix from porcine SIS is an example of a biomaterial capable of recruiting a population of stem cells to participate in the tendon remodeling [81].

There are additional factors other than scaffold material which impact the scaffold's ability to effectively deliver stem cells. For example, if cell-to-collagen ratio is too high, the cells can become damaged by excessive cell traction forces [34]. Finding the optimal cell-to-collagen ratio could improve the delivery of stem cells to the healing tendon. In addition to the concentration of ECM components, the precise spatial arrangement of the molecules affects the delivery of MSCs. The spatial arrangement of collagen fibrils can be modified by the angle at which tendinous scaffolds are carved. Longitudinal tendon slicing promotes favorable seeded-cell morphogenesis and differentiation [71].

A study conducted by Pietschmann et al. [58] showed that scaffolds seeded with MSCs may be less effective than scaffolds loaded with tenocytes. Sixteen weeks after repair, rat Achilles tendons treated with scaffolds seeded with tenocytes

had greater failure strength/cross-section ratio than those treated with scaffolds seeded with MSCs or controls.

Growth factors

Basic fibroblast growth factor

Basic fibroblast growth factor (bFGF) has the ability to increase collagen type I and type III production which has led to interest in its use in tendon-healing therapy. In intrinsic tendon healing leading to scar formation, there is an altered type I: type III collagen ratio. Strategies to improve the native tissue collagen ratios is a goal of functional tendon repair. However, lentiviral bFGF transduction combined with MSCs in an animal model had negligible effects on tendon remodeling. A possible explanation is the ability of MSCs alone to produce sufficient bFGF required for tendon remodeling making the additional bFGF transduction unnecessary [41].

Hepatocyte growth factor

Hepatocyte growth factor (HGF) is found in PRP and is known to have anti-inflammatory effects. In vitro and in vivo animal studies have suggested the anti-inflammatory effects of PRP are a result of the high concentration of HGF [82]. It is hypothesized that HGF can reduce scar formation in tendon healing by inhibiting the overexpression of ECM and reducing transforming growth factor beta-1 (TGF-β1)-induced myofibroblast differentiation. These effects of HGF have been demonstrated in a rat Achilles tendon model [12].

Recombinant human platelet-derived growth factor-BB

Recombinant human platelet-derived growth factor-BB (rhPDGF-BB) accelerates tendon healing through a variety of mechanisms. In ruptured tendon animal models, rhPDGF-BB improves mechanical strength and range of motion through increased matrix remodeling, collagen synthesis, vascularity, and cell proliferation [65, 13]. Its effects are thought to be best when administered over time which has created interest in the development of a delivery method that will allow for optimum doses over the right time period into the site of repair. Promising methods of delivery include rhPDGF-BB-coated sutures and mesoporous silica nanoparticles (MSN) [13, 70].

Transforming growth factor-β

Transforming growth factor-β (TGF-β) regulates the differentiation and proliferation of cells and causes an increase in collagen I and collagen III production from tendon cells. Collagen fibers are largely responsible for the mechanical strength of the healing tendon making treatment with TGF-β an important area of investigation [30]. Treatment with TGF-beta1 cDNA-transduced BMSCs grafts, injections of TGF-β, and delivery of TGF-β by adenovirus-modified muscle grafts have shown promising results in rat Achilles tendon models [47, 35, 29]. As early as 2 weeks postoperatively, the repaired tissue treated with TGF-β has histological appearance similar to that of native tendon [47]. TGF-β therapy can increase mechanical strength of the healing Achilles tendon by the regulation of collagen synthesis, up-regulation of cross-link formation, and enhanced matrix remodeling [29].

Interleukin-6

The ability of interleukin-6 (IL-6) to stimulate the synthesis of collagen has led to the consideration of IL-6 acting as a growth factor. The interstitial concentrations of IL-6 in the peritendinous region around the Achilles tendon increase drastically upon exercise, or mechanical loading. This led to an interest in IL-6's ability to transform mechanical loading into collagen synthesis. In vivo study found that the infusion of IL-6 into the peritendinous tissue around the Achilles tendon resulted in increased local collagen synthesis with or without exercise [2]. Future studies should consider the use of IL-6 for Achilles tendon repair and the effects of mechanical stimulation on biomaterials used for repair.

Combinatory use of growth factors

Several of the growth factors previously discussed in addition to others such as VEGF, cartilage-derived morphogenetic protein-2 (CDMP-2), and insulin-like growth factor-1 (IGF-1) have shown positive effects when applied individually to Achilles tendons using a variety of delivery methods [3, 75]. Konerding et al. [40] hypothesized an improvement of long-term outcomes in Achilles tendon repair from the use of the short-term application of key mitogenic and angiogenic growth factors in a rabbit model. However, the use of VEGF, bFGF, and PDGF administered peritendinously had only a marginal impact on the therapeutic outcome of Achilles tendon repair. The dosing and timing of the growth factors used are possible reasons for their minimal effects. All three of the chosen growth factors also require heparin sulfate proteoglycans (HSPG) in order to bind to their respective receptors. The effects of injury on HSPGs may cause exogenous growth factor therapy to become an ineffective treatment.

Discussion

The appropriate treatment for Achilles tendon ruptures and chronic Achilles tendinopathies remains a clinical challenge.

Despite major advances in surgical procedures and techniques in other areas of orthopedics, the approach to treatment of the Achilles tendon seems to lag behind. Biological augmentations have shown promising results in their application to a variety of pathologies and may be an integral part of optimizing Achilles tendon healing and repair. However, most of this is lab research, and we are still awaiting clinical trials to evaluate efficacy in vivo.

Platelet-rich plasma is capable of improving the healing process of Achilles tendon ruptures as evidenced by numerous studies including clinical trials. However, a majority of studies show that there remains insufficient evidence to support the use of PRP in the treatment of chronic Achilles tendinopathies.

The mechanism by which PRP is believed to accelerate healing involves its high concentration of growth factors. The use of growth factors such as HGF, rhPDGF-BB, IL-6, and TGF-β in Achilles tendon repair has shown promising results. Bone morphogenetic proteins such as BMP-12, BMP-2, BMP-7, and BMP-14 have also shown positive results for the biological augmentation of Achilles tendon repair. In vitro and preclinical studies have indicated the potential effectiveness of bone marrow aspirate as well. The further investigation of these techniques in a clinical setting is warranted.

The way in which several of these techniques are implemented involves the use of a scaffold material. Finding an ideal biomaterial for Achilles tendon scaffolds remains an area of investigation. PHA, decellularized tendon tissue, and porcine SIS are examples of biomaterials which have been shown to accelerate Achilles tendon healing. The ability to deliver stem cells or promote the migration of stem cells is potentially an important property for scaffolds to possess. Substantial evidence supports the positive effects of stem cells on the early phases of Achilles tendon healing.

The combination of different areas of biologics may be useful in order to optimize the benefits of these techniques. For example, bioscaffolds seeded with stem cells and stem cells genetically engineered to produce specific growth factors have successfully improved tendon repair. However, the complexity of some of the pathways involved in biological augmentation continues to remain a challenge in understanding their interactions in vivo. Future investigation should focus on finding an ideal combination of these techniques suitable for clinical application.

Compliance with Ethics Guidelines

Conflict of Interest Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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