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Review Article

Current advances in the treatment of medial and lateral epicondylitis

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ABSTRACT

Despite advances elucidating the causes of lateral and medial epicondylitis, the standard of care remains conservative management with NSAIDs, physical therapy, bracing, and rest. Scar tissue formation provoked by conservative management creates a tendon lacking the biomechanical properties and mechanical strength of normal tendon. The following review analyzes novel therapies to regenerate tendon and regain function in patients with epicondylitis. These treatments include PRP injection, BMAC, collagen-producing cell injection, and stem cell treatments. While these treatments are in early stages of investigation, they may warrant further consideration based on prospects of pain alleviation, function enhancement, and improved healing.

1. Introduction

Epicondylitis is a prevalent disorder of the arm that affects men and women equally, predominantly between the ages of 45 and 54 years.[1] Epicondylitis is characterized by functional impairment and chronic pain in the region of the epicondyle, incited by resisted use of the flexor or extensor muscles of the wrist.[2] Medial epicondylitis, colloquially known as “golfer’s elbow,” is provoked by frequent eccentric loads on the muscles that are responsible for forearm pronation and wrist flexion. This repetitive stress leads to microtrauma of the common flexor tendon and debilitating, chronic pain at the epicondyle. Lateral epicondylitis, or “tennis elbow,” is more prevalent than its medial counterpart, affecting 1.3% of the general population as opposed to 0.4%.[1] Lateral epicondylitis is caused by repetitive strain to the extensor tendon, notably extensor carpi radialis brevis, or by forced extension or direct trauma to the lateral epicondyle. Both medial and lateral epicondylitis were historically classified as inflammatory disorders, resulting in conservative pain management with anti-inflammatory drug administration, physical therapy, rest, and steroid injections with variable long-term success.[3] The scar tissue formation provoked by conservative management creates a tendon lacking the biomechanical properties and mechanical strength of an undamaged tendon.[4]

While the specific causes of epicondylitis have not been elucidated, the tendinosis is now thought to occur via a degenerative mechanism, which leads to calcification, fibrosis, vascular proliferation, and hyaline degeneration of the affected muscles without inflammatory infiltration. Due to this new understanding of epicondylitis, treatment approaches have shifted toward novel biological therapies aimed at tendon regeneration rather than pain management.[4] The developing treatment strategies include injection of platelet-rich plasma (PRP), collagen-producing tenocyte-like cells, or various types of stem cells at the site of the tendon lesion. Platelets contain alpha granules with many growth factors that promote growth and repair of damaged tissue.[5] Such a high concentration of growth factors has the potential to aid in tissue healing and alter the biomechanical and histological properties of the affected tendon. Tenocyte-like cells and stem cells also attempt to restore normal biologic properties to the tendon by promoting collagen synthesis and muscle repair. The following literature review aims to examine the safety and efficacy of these novel treatments related to medial or lateral epicondylitis.

1.1. Platelet rich plasma (PRP)

PRP, an autologous preparation of whole blood, filtered to achieve a fraction of plasma containing supraphysiologic concentrations of platelets, has gained traction for its use in the treatment of musculoskeletal injury[6] Platelets play a central role in hemostasis and tissue healing, secondary to the numerous growth and differentiation factors they secrete, including: platelet derived growth factor (PDGF), transforming growth factor (TGF), platelet factor 4 (PF4), interleukin-1 (IL-1), platelet-derived angiogenesis factor (PDAF), vascular endothelial growth factor (VEGF), and more [7,8] Though the specific downstream effects of these growth factors, cytokines, and chemokines have not been completely elucidated, ultimately these pathways induce the synthesis of proteins necessary for collagen, osteoid, and extracellular matrix formation. Lastly, PRP hosts numerous cell adhesion molecules including fibrin, fibronectin, vitronectin, and thrombospondin, that stimulate the

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assemblance of osteoblastic, fibroblastic, and epithelial cells, which comprise the natural microenvironment of host tissue.[9,10]

Beck, et al.,[5] examined the efficacy of PRP in rotator cuff repairs by creating tendon-from-bone supraspinatus tears and performing transosseous repairs in rats. PRP was administered at the site of surgery in the treatment group, but the control group did not receive PRP augmentation. Tendons were assessed for load failure, stiffness, and failure strain at 7, 14, and 21 days after the experiment. At day 7, the control group showed increased failure strain, but no difference in failure load and stiffness compared to the treatment group. Histologically, the PRP group showed increased focal fibrinoid necrosis in the tendon, which is likely the cause of the decreased failure strain. At day 7 and 14, the treatment group showed hypertrophic chondrocytes with a basophilic matrix that likely represents increased glycosaminoglycans production by the chondrocytes. At day 21, the control group had increased stiffness, decreased failure strain, but no difference in failure load compared to the treatment group. Histologically, at day 21 the treatment group had more linear, large, and organized collagen fibers. The study found that PRP changed tissue properties of the rotator cuff tendon without improving the tendon-to-bone failure load.[5]

Kon, et al.,[11] described the immense variations platelet-rich plasma (PRP) treatment protocols. Preparation method, formulation, cell content, storage modalities, activation methods, therapeutic protocols, and the disease phase treated are variables that lead to discrepancies when comparing *in vivo* and *in vitro* studies involving PRP augmentation. Because few high-quality randomized trials have been published, Kon, et al.,[11] does not endorse this approach for clinical practice but acknowledges the exciting possibilities for further work.[11] Research from Mautner, et al.,[12] expands on these variables, also citing platelet count, presence of leukocytes, activators, solution pH, delivery method, and rehabilitation procedures as important factors that must be considered. Mautner proposes that higher platelet counts with leukocytes and a slightly acidic pH injection is ideal to promote the healing of tendons.[12]

In an analysis by Halpern et al.,[13] PRP efficacy was analyzed and challenged in a number of musculoskeletal studies. Thus, it was evaluated that the treatment is was significantly effective in treating lateral and medial epicondylitis, and futhermore, a practical alternative for surgical intervention. Beyond it's clinical efficacy in structural healing, PRP healing has been linked to reduced need for narcotics, improved sleep, and reduction in perception in pain.[13] As a result, it can be deduced that PRP treatment is not only effective in recovery of structure and function of the lateral and medial epicondyles, but rather, improves quality of life through the recovery process.

The rising use of PRP treatments in acute and chronic tendon, ligament, and muscle injuries in athletes led to concern within the World Anti-Doping Agency over the performance-enhancing growth factors contained within the autologous blood product. Wasterlain, et al.,[14] investigated the effect of PRP injection on systemic growth factors with performance-enhancing effects. They tested levels of hGH, bFGF, IGF-1, VEGF, IGFB*P*-3, and PDGF-BB in 25 patients who underwent intratendinous leukocyte-rich PRP injection at baseline, 0.25, 3, 24, 48, 72, and 96 h after the injection. Wasterlain, et al.,[14] found a significant increase in IGF-1, VEGF, and bFGF, all of which have performance-enhancing potential.[14] Another study by El-Sharkaway et al.[15] confirmed the increase in growth factors by comparing groups treated with PRP with those treated with platelet-poor plasma or whole blood transfers.[15]

Zhang, et al.,[16] compared the effects of pure platelet rich plasma PRP (P-PRP) and leukocyte rich PRP (L-PRP) treatments on the differentiation of tendon stem cells (TSCs).[16] They demonstrated that L-PRP stimulated lower levels of vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), transforming growth factor (TGF-beta), and platelet derived growth factor (PDGF) compared to P-PRP. P-PRP solutions also stimulated more TSC proliferation. The TSCs grown in P-PRP culture produced more collagen and formed tendon-like tissue while the TSCs grown in L-PRP matured into non-tenocytes and produced inflammatory factors that stimulated increased apoptosis.[16]

1.2. Bone marrow aspirate concentrate

Bone marrow aspirate concentrate (BMAC) is an emerging, novel treatment for various bone and cartilage pathology and injury. Similar to other orthobiologic intra-articular injections like hyaluronic acid and PRP, BMAC gives patients the opportunity to restore the natural microenvironment of their damaged or diseased tissue. Bone marrow concentrate is commonly taken from pelvic bone, and contains mesenchymal and hematopoetic stem cells, platelets, growth factors, cytokines, and anti-inflammatory and immunomodulatory cells.[17] While there are numerous preclinical research papers on the efficacy of mesenchymal stem cells for cartilage defect regeneration, there remains a paucity of high-quality, randomized controlled clinical trials.[18] In recent years, several systematic reviews investigating the use of BMAC on osteochondral lesions of the talus, and chondral injuries and osteoarthritis of the knee, have supported the potential of BMAC in regenerative medicine, despite a limited number of randomized, controlled trials.[19,20]

Further evaluating the efficacy of bone marrow injections, thirty patients who were untreated for Lateral Epicondylitis were evaluated with the Patient-rated Tennis Elbow Evaluation (PRTEE) prior to and following the treatment of a single administration of Iliac Bone Marrow Aspirate.[21] This concentrate, composed of iliac BMA centrifuged for 20–30 min at 2000 RPM, was effective in simplicity and safety, avoiding further complications as other modes of treatment. Evaluated at 2, 6, and 12 weeks after administration, these patients showed drastic improvement in the two week evaluations, thus showing the efficacy of this treatment's recovery time. Although Singh et al.[21] explained the limitation of their study in long term treatment, they believe that this treatment, when paired with growth factor and other stem cell treatment, can be an effective alternative in lieu of surgery.[21]

1.3. Direct tenocyte injecton

Autologous tenocyte injection (ATI) is another option for non-operative management of lateral and medial epicondylitis. As a result of the poor cellularity and vascular supply of tendons, particularly at regions of bony pulleys, tendon regeneration following injury is usually poor and large areas of scar tissue can develop.[22] ATI is a two-step process whereby a small number of tenocytes are harvested, typically from the patellar tendon, cultured, and subsequently injected into the injured tendon. Though the number of quality, randomized, clinical trials is limited, several studies have shown utility of ATI for treatment of tendinopathies including gluteal tendinopathy and Achilles tendinopathy.[23–25]

A prospective clinical pilot by Connell, et al.,[4] used collagen-producing cells derived from dermal fibroblasts to treat refractory lateral epicondylitis in twelve patients. The clinicians used ultrasonography guidance to inject cells into the common extensor origin at the site of tear and fibrillar discontinuity. Pain severity and functional disability were evaluated with the Patient-Rate Tennis Elbow Evaluation (PRTEE) scale, and tendon-healing response was measured on ultrasonography based on tendon thickness, hypoechogenicity, intrasubstance tears, and neovascularity. The median PRTEE score decreased significantly at 6 weeks, 3 months, and 12 months after procedure and ultrasonography showed a decrease in the number of tears, number of new vessels, and tendon thickness in 11 out of 12 patients. Connell, et al.,[4] concluded that skin-derived tenocyte-like cells can be injected safely into patients and have a therapeutic effect in patients with refractory lateral epicondylitis.[4]

Based on the success of skin-derived tenocyte cell injection in lateral epicondylitis by Connell, et al.,[4] Clarke, et al.,[26] performed a double blind randomized control trial on 46 patients with refractory patellar tendinopathy. The patients were divided into one group who received

laboratory-amplified tenocyte-like cells injected into the site of hypoechogenicity and intrasubstance tear while the second group received an injection with autologous plasma alone. Patients were analyzed with the Victorian Institute of Sport Assessment (VISA) scale. As hypothesized based on the data from Connell, et al.,[4] the group who received an injection with collagen-producing tenocyte-like cells improved significantly faster and with greater overall improvement in pain and function than the group who received injections with plasma.[4,26]

Wang, et al.,[27] examined the long-term efficacy and safety of ultrasound-guided autologous tenocyte injection (ATI) treatments. Fifteen patients were followed for a mean of 4.5 years post-ATI. Wang, et al.,[27] reported a 78 percent pain and function score improvement between the initial assessment of the patient and the final follow up with zero complications, adverse effects, or infections after 4.5 years. Wang, et al.,[27] reported improved scores in clinical function, VAS pain, and MRI tendinopathy for at least five years in patients diagnosed with chronic resistant lateral epicondylitis.[27]

Zhang, et al.,[16] presented the histopathological characteristics of tendinopathy, explored the cellular and molecular cues in the pathogenesis of tendinopathy, and described the potential application of tendon stem/progenitor cells (TSPCs) in chronic tendon injuries. Current evidence suggests that the pathogenesis of tendinopathy arises from the absence or misregulation of TSPCs. Based on such evidence, Zhang, et al.,[16] proposed exogenous TSPCs or regulation of endogenous TSPCs as targets for biologic management of various tendinopathies, such as medial and lateral epicondylitis.[16]

Lee, et al.,[28] examined the therapeutic value and safety of allogeneic adispose-derived mesenchymal stem cells (allo-ASC) in the treatment of lateral epicondylitis. Their study included 12 patients diagnosed with chronic lateral epicondylitis. Half of the participants were given injections of allo-ASC directly into the lesions of the common extensor tendon. Each participant was evaluated after 2, 6, 12, 26, and 52 weeks post-injection. The Visual Analog Scale (VAS) for elbow pain, a modified Mayo clinic performance index for the elbow, and ultrasound images of the tendon were used as measures of tendon health. Along with zero adverse effects from the allo-ASC treatment, Lee, et al.,[28] reported that patients' VAS scores decreased (66.8 mm to 14.8 mm), elbow performance scores improved (64.0 to 90.6), and tendon defects decreased over the 52-week period in both groups.[28]

Oshita, et al.,[29] investigated the effects of adipose-derived stem cells on tendon healing in a rat tendinopathy model. The researchers induced tendinopathy in 16 rats by injecting collagenase into the Achilles tendon. After one week, the treatment group was given adipose-derived stem cells (ASC) while the control group was given phosphate-buffered saline. The animals were sacrificed and the tendons analyzed at 4 weeks and 12 weeks post-injection. The degree of degeneration in the tendon was evaluated using the Bonar scale and the microstructure of healing tendons was observed via scanning electron microscopy. RT-PCR was performed on the tissue to determine the ratio of type III collagen to type I collagen. The results demonstrated a lower degree of degeneration in the treatment group compared to the control group at both time points and the RT-PCR showed a lower ratio of type III collagen to type I collagen in the treatment group.[29]

2. Discussion

The prevalence of medial and lateral epicondylitis in the general public and in athletes is high, causing many people to face occupational and sporting disability that severely impairs their quality of life. Promising new studies utilizing emerging biologics may provide more effective regenerative therapies than conservative treatments have traditionally allowed.

PRP augmentation at lesion sites is an exciting front in the quest to regenerate tendon rather than ameliorate symptoms. However, as Kon, et al.,[11] and Mautner, et al.,[11] report, the high variability in protocols and inconsistent human clinical trials leave room for pause in advocating this new treatment as standard for patients with lateral and medial epicondylitis.[11,12] The large number of growth factors stimulated by PRP administration is another point of contention in recommending this therapy to athletes who are restricted by the WADA. While L-PRP stimulates growth factors to a much lesser degree than P-PRP, which may be appealing to athletes hoping to stay in WADA guidelines, L-PRP infringes on the differentiation and successful maturation of TSPCs.[16] The lack of general empirical evidence and randomized, controlled, human clinical trials preclude clinicians from accepting PRP augmentation as an acceptable treatment alternative to conservative management.

Aside from PRP injection and stimulation of growth factors, another form of biologic enhancement comes in the form of tenocyte-like collagen producing cells. Connell, et al., demonstrated that collagen-producing cells derived from dermal fibroblasts successfully and safely diminished pain and reduced functional disability in patients with refractory lateral epicondylitis. The success of Connell's prospective clinical study led to the randomized controlled trial by Clarke, et al.[26] Clarke, et al., examined refractory patellar tendinosis, which has a similar histologic profile to lateral and medial epicondylitis, both with collagen fibrillar degeneration and angiofibroblastic proliferation.[4,26,30] Angiofibroblastic tendinosis is characterized by a degenerative, non-inflammatory disease etiology with disorganized collagen and immature fibroblasts and neovascularization.[31] The enhanced and expedited improvement in pain and function in patients who received injections of collagen-producing cells derived from dermal fibroblasts reported by Clarke, et al.[26] is promising for application of the same treatment to patients with lateral and medial epicondylitis. Wang, et al.,[27] furthered support for the treatment of tendinosis with injection of collagen-producing cells by reporting zero complications and sustained improvement in clinical function, reduction in pain, and improved MRI reports in patients at a mean follow-up of 4.5 years.[27] However, the autologous tenocytes utilized by Wang were derived from patellar tendon biopsies, whereas the collagen-producing tenocyte-like cells used by Connell and Clarke were derived from dermal fibroblasts. While the utilization of collagen producing cells is gaining momentum, randomized control trials comparing these treatments to standard conservative measures is needed.

A greater understanding of the role of TSPCs in tendon healing provides a solid foundation for further research into the utilization of stem cells in tendinopathies. Zhang, et al.,[16] provided a holistic picture of the cellular cues that are necessary for proper differentiation of TSPCs.[16] Oshita, et al.,[29] demonstrated the efficacy of injections of adipose-derived stem cells in a rat tendinopathy model. The Oshita, et al.,[29] study support the use of stem cells in tendinopathies, citing less degeneration of the tendon and a normalized collagen ratio in the animals that received stem cells.[29] Lee, et al.,[28] performed experiments validating the utility and safety of adipose-derived mesenchymal stem cells in patients with lateral epicondylitis. Injections of stem cells into the common extensor origin led to enhanced performance, decreased pain, and decreased tendon deficits seen on ultrasound.[28]

2.1. Future research

Future research should focus further on biologic therapies encompassing the three novel therapies presented in this review. PRP treatments are currently in the early stages development, but are considered more sophisticated than the current standard of care. Implications for research with PRP treatments should focus on narrowing down the factors involved in creating an evidence-based protocol for the use of PRP. While the extensive variables inherent to PRP augmentation present complications in the replication of results, injection of either collagen producing cells or stem cells might be a more promising and fruitful approach to regenerating tendon tissue in patients with chronic medial and lateral epicondylitis.

3. Conclusion

An effective long-term solution for patients who experience medial and lateral epicondylitis would relieve pain for a significant portion of the population and reduce the costs of managing a chronic condition for the healthcare system. The empirical evidence for new treatments for epicondylitis is under development, and initial research supports continuing to optimize PRP variables, collagen-producing cell treatments, and stem cell treatments. Voids in the literature, particularly regarding PRP protocols, prohibit the recommendation that these treatments are safe and effective at this time. However, the preliminary results of initial clinical trials both in humans and in animals suggest that collagen-producing cell treatments and stem cell treatments have the potential to be more effective for tendon healing, pain management, and restoration of use than surgical techniques or conservative therapies alone.

Conflict of interest

None.

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