Systematic Review

Muscle and Tendon Injuries: The Role of Biological Interventions to Promote and Assist Healing and Recovery

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Purpose: To summarize clinical studies after platelet-rich plasma (PRP) therapy for tendinopathy, plantar fasciopathy, and muscle injuries; to review PRP formulations used across studies; and to identify knowledge deficits that require further investigation. **Methods:** After a systematic review in PubMed, we identified clinical studies assessing PRP efficacy in tendon and muscle during the past decade. We standardized data extraction by grouping studies based on anatomic location; summarized patient populations, PRP formulations, and clinical outcomes; and identified knowledge deficits that require further investigation. **Results:** Overall, 1,541 patients had been treated with PRP in 58 clinical studies; of these, 26 addressed upper limb tendinopathies and 32 addressed the lower limb (810 patients and 731 patients treated with PRP, respectively). The quality of research is higher for the upper limb than for the lower limb (23 controlled studies, of which 17 are Level I, *v* 19 controlled studies, of which 6 are Level I, respectively). Patients have been treated mostly with leukocyte-platelet–rich plasma, except in the arthroscopic management of the rotator cuff. The safety and efficacy of PRP for muscle injuries has been addressed in 7 studies including 182 patients. Differences across results are mainly attributed to dissimilarities between tissues and different stages of degeneration, numbers of PRP applications, and protocols. **Conclusions:** Given the heterogeneity in tendons and tendinopathies, currently, we are not able to decide whether PRP therapies are useful. Despite advances in PRP science, data are insufficient and there is a clear need to optimize protocols and obtain more high-quality clinical data in both tendinopathies and muscle injuries before making treatment recommendations. **Level of Evidence:** Level IV, systematic review of Level I through IV studies.

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The current demographic changes in developed countries, including Europe and United States, are producing an alarming burden of degenerative musculoskeletal conditions. Though not as pervasive as osteoarticular conditions, tendinopathies are insidious. Because of its expanding prevalence, tendon pathology is becoming a major focus for research aiming to elucidate its cause and pathogenesis and to identify minimally invasive biological interventions.[1]

It is incumbent on anyone interested in implementing biological interventions such as platelet-rich plasma (PRP) or cell therapies to understand the characteristics and the rationale for their application to identify hurdles to achieve successful tissue repair.[2] How to intervene biologically is chiefly driven by our understanding of the pathologic processes underlying the condition; thus basic hypotheses are shared in both PRP and cell therapies. In tendinopathy the failed-healing hypothesis suggests that repetitive stresses lead to small injuries within the tendon that fail to heal before further trauma occurs. Difficulties in achieving healing arise in tissues characterized by a low cell number and low extracellular matrix turnover.[3]

Thus, broadly speaking, tendon regeneration can be achieved by increasing cell numbers and/or enhancing tendon cell anabolism (collagen synthesis). As a dominant cell type in tendons, tenocytes are responsive to molecular environmental stimuli that modulate

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proliferation and collagen synthesis. Biological therapies, such as cell therapies, are designed to augment cell numbers in the injured tissue by exogenous expansion and grafting. Two biotechnology companies are at the forefront of cell product development for tendons. An autologous tenocyte therapy—Ortho-ATI—is currently available from Orthocell, Murdoch, Australia, and a phase I/II double-blind randomized trial is planned in the Netherlands (NCT01343836). In addition, autologous dermal fibroblasts are manufactured by Innovacell Biotechnologie AG, Innsbruck, Austria, and have been explored for tendon augmentation based on their collagen-producing capabilities. A systematic literature review of human studies of cell therapy in tendons[4] disclosed 4 clinical studies. Three of these, sponsored by Innovacell, examined skin fibroblast injections in 3 anatomic locations—elbow,[5] patellar,[6] and Achilles tendons[7]—showing safety and potential benefits in the short-term. In addition, human bone marrow mesenchymal stem cells have been safely injected in rotator cuff tears with promising results in a limited number of patients.[8] The field remains otherwise under-researched.

Alternatively, PRP therapies, designed to modify the biological milieu and target tenocyte activation, have been explored in both experimental and clinical studies. Previous research has shown that tenocytes from tendinopathic tissue, when exposed to PRP releasates, proliferate and synthesize extracellular matrix molecules (including type I, II, and X collagen; decorin; aggrecan; and biglycan), essential to tendon function.[9,10] Moreover, PRP provides protection against oxidative stress and modulates the angiogenic and inflammatory conditions of tendons, as well as the anabolic capabilities of tenocytes.[11,12] Several signaling proteins released from PRPs induce neotendon formation, including fibroblast growth factor 2, transforming growth factor β, insulin-like growth factor 1, vascular endothelial growth factor, platelet-derived growth factor, and bone morphogenetic protein 2.[2] PRP enhances tendon cell growth and migratory capacity and combats the oxidative stress leading to cell apoptosis.[13,14]

PRP can enhance the self-healing potential of tissues by proper activation of endogenous local stem cells. Though relatively low in number, tendon stem cells (TSCs) also play a critical role in tendon regeneration because of their ability to self-renew and differentiate into tenocytes, thereby replacing tenocytes lost from apoptosis.[15] Importantly, the number of TSCs may be reduced in tendinopathy, and the TSCs may differentiate into non-tendon cells.[16] Migration and tenogenic differentiation of PRP-treated tendon precursor cells are currently emphasized by experimental studies.[17,18]

Other than increasing cell numbers and differentiation, PRP enhances tendon regeneration by improving cell anabolism.[2] Recent estimates of the rate of replacement for collagen in the Achilles tendon concluded that tendon tissue is practically inert.[19] Quite the opposite, the muscle tissue (musculus psoas major), used as a comparator in this study, exhibits high turnover rates (i.e., is constantly being replaced).

The biological mechanisms underlying muscle regeneration are similar, but in this context PRP aims primarily to potentiate migration and differentiation of satellite cells while modulating inflammation, in doing so tailoring the microenvironment for efficient repair.[20,21] Although experimental research supports PRP intervention in tendons and muscles, there is a clear need (1) to summarize clinical results after PRP therapy for tendinopathy and muscle injuries, (2) to review PRP formulations used across studies, (3) to provide treatment recommendations based on the protocols described in the best available literature, and (4) to identify knowledge deficits that require further investigation.

Methods

Search for Clinical Data

We searched Medline via PubMed with combinations of the search terms "platelet rich plasma," "tendon," "rotator cuff," "epicondylitis," "fasciitis," "Achilles," "patellar," "skeletal muscle," "muscle injuries," "sports," and "human" from January 2003 to August 2014. We also searched our own files. Only articles published in English were reviewed.

Study Selection and Data Extraction

We included all original articles describing the use of PRP in tendon and muscle injuries. All types of management (i.e., conservative, arthroscopic surgery, or open surgery) and controlled and uncontrolled studies were included. Conference proceedings and case reports were excluded.

We extracted and tabulated the following data: study design, type of participants, type of intervention (i.e., PRP formulation and number of injections), follow-up, and type of outcome measures. Results were synthesized by grouping the studies based on anatomic locations as upper limb lesions, including epicondylitis and rotator cuff conditions, and lower limb, including the patellar tendon, Achilles tendon, and plantar fascia.

Results

Upper Limb Tendon Injuries

Overall, in the reviewed clinical studies, 1,541 patients were treated for tendinopathy (including plantar fasciitis). Most research focused on upper limb pathology, with 9 controlled studies[22-30] and 2 case series on epicondylitis,[31,32] 13 controlled studies on arthroscopic management of the rotator cuff,[33-45] 2 controlled studies evaluating conservative management,[46,47] and 1 case series[48] (Table 1).