Orthobiologics: Tendinopathy

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Introduction

Tendinopathy refers to a complex pathology of the tendon, characterised by pain, functional impairment and reduced ability to exercise[1]. Despite recent advances in our understanding of this condition, tendinopathy remains challenging to treat. While active rehabilitation through exercise remains the cornerstone of management there is increasing interest in new orthobiologic and regenerative therapies, some of which have shown promise in pre-clinical and clinical settings. These therapies will be particularly important for the 30–50% of patients who do not respond to targeted exercise programs[2]. At present orthobiologic therapies are frequently applied without explicit understanding of how these treatments may produce a therapeutic effect in a specific patient group. The development of new therapies for tendinopathy will be guided by increasing understanding of the underlying disease process.

Epidemiology

The prevalence of tendinopathy has increased worldwide over the last two decades, with a wide range of intrinsic and extrinsic risk factors identified including increasing age, female sex, metabolic disorders (diabetes, hyperlipidaemia, obesity), medications (fluoroquinolones, statins, hormone replacement therapy) and sporting and occupational factors. The most common sites affected include the shoulder (supraspinatus), elbow (common flexors and extensors) heel (plantar fascia and Achilles tendon), greater trochanter (gluteal insertional complex), knee (patellar tendon) and ankle (tibialis posterior tendon)[3]. The incidence of lower limb tendinopathy exceeds that of arthritis (10.5 vs 8.4 per 1,000 person-years)[3], and tendinopathy accounts for ~30% of injuries in elite athletes[4].

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The pathophysiology of tendinopathy

The pathogenesis of tendinopathy is multifaceted and complex, and scientific understanding is evolving. Repetitive tendon overload is thought to lead to injury of the microscopic collagen fibrils. Under normal circumstances, early tendon matrix injury prompts an effective healing process. However, inadequate intrinsic healing capacity of the tendon, or insufficient time to recover, can lead to an accumulation of matrix damage[1]. These initial structural alterations can remain subclinical and patients may have no symptoms. However, as damage progresses, there is an accumulation of secreted cytokines and inflammatory mediators, and activation of nociceptors leading to the development of symptoms. As repair mechanisms become overwhelmed and dysregulated, tendinopathy becomes established and chronic. Several factors that contribute to, or are associated with the development of tendinopathy have been identified. These include extracellular matrix dysregulation, interfascicular matrix changes, non-collagenous matrix alterations, oxidative injury, apoptotic pathways, molecular inflammation, microRNAs, resolution pathways and inflammatory cytokines[5]. Understanding these critical pathways offers the potential for developing targeted therapies (Figure 1).

Management

Individually tailored exercise programmes remain the most effective approach in the treatment of tendinopathy. While prolonged periods of exercise based treatment is frequently required to yield improvements, not all patients respond satisfactorily, and other treatment options are widely used as adjuncts or alternatives. Non-biologic adjuncts to exercise include corticosteroid injections, glyceryl trinitrate, high volume saline injections, low energy laser and shockwave therapy. These strategies are generally applied with the aim of reducing the local molecular inflammatory response driving tendinopathy, with varying levels of effectiveness[5-8]. Surgery typically involving excision of the degenerative tendon, debridement of adhesions and decompression of the tendon is considered a last resort[9]. More recently, there has been increasing interest in orthobiologic therapies, some of which have shown promise in pre-clinical and clinical settings.

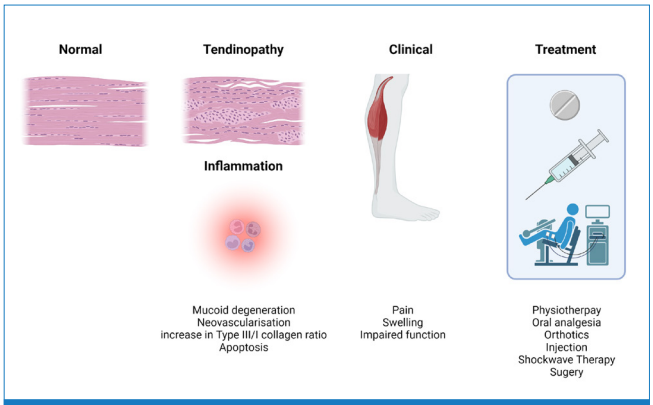

Figure 1: Overview of the pathogenesis, clinical features and treatment options for tendinopathy. *Created with BioRender.com.*

Orthobiologic strategies

Two of the most widely studied orthobiologics in the management of tendinopathy are platelet-rich plasma (PRP) and cell therapies.

PRP: Several factors present in PRP are recognised to be involved in different phases of tendon healing (including TGFβ, PDGF, bFGF, VEGF, IGF1 and EGF) or to have immunomodulatory effects. As such, the delivery of high concentrations of these factors could potentially support healing of tendon tissue, whilst tempering local inflammation[10]. The results of clinical studies to date have been varied[11]. A major challenge of research in this area is the considerable heterogeneity in patients, PRP preparations, techniques of administration and outcome measures. In addition, the inadequate reporting of protocols, formulations and outcomes limits interpretation of data, comparison between studies and the ability to replicate experimental conditions[12]. In the setting of lateral epicondylitis, several prospective randomised control trials have reported leukocyte rich (LR-PRP) injections result in a significant improvement in pain over controls[13,14]. However, the value of PRP in this setting is not universally agreed with systematic reviews and meta-analyses drawing conflicting conclusions[15-17]. Similarly, systematic reviews report contrasting results in comparative investigations evaluating PRP and placebo or other treatments for patella tendinopathy, although there are a large number of case series reporting significant improvements in pain and function in the short and long term[18,19]. In general, PRP has not been demonstrated to be effective in systematic reviews evaluating treatment for Achilles tendinopathy[20,21]. Mixed results following the use of PRP for treating rotator cuff tendinopathy have been reported[22-24], with one study suggesting an increased rate of apoptosis in cuff tendinopathy treated with PRP[25]. Despite more clinical evidence for LR-PRP formulations over leukocyte-poor preparations in a number of settings[26,27], it can be associated with increased initial post-procedure discomfort over leukocyte poor-PRP[28].

Cellular therapies: There is increasing interest in the use of autologous cells (typically from bone marrow or fat) and autologous tenocytes to treat tendinopathy. Cells have been evaluated in small clinical studies of Achilles tendinopathy, lateral elbow tendinopathy, patellar tendinopathy and rotator cuff tendinopathy[29], although the majority have been level III and IV studies. In an RCT comparing the effect of intra-tendinous PRP with allogeneic-adipose derived cells in patients with Achilles tendinopathy, both treatment groups showed reduced pain and improved physical function scores at six months[30]. Several small case series and pilot studies have reported positive results with autologous tenocyte injections in the setting of rotator cuff, gluteal and, elbow tendinopathy and higher order evidence is now required to evaluate effectiveness of these strategies[30].

Future therapies

Integrating advances in basic science understanding and clinical research data to provide a comprehensive picture of the disease process involved in tendinopathy is likely to accelerate the development of successful future treatments[1]. There are now a number of pharmacological treatment approaches in early phase trials that seek to exploit recent advances in understanding of pathogenesis through cytokine manipulation, targeting of resolution and microRNA molecules, epigenetic modification and modulation of various signalling pathways (such as IL-17A, Wnt and NF-κB)[1,5]. Tissue engineering and gene delivery approaches, whereby exogenous genetic material is inserted into cells with the aim of inducing, silencing, upregulating or downregulating the expression profile and secretion of proteins show promise in pre-clinical studies[31].

Conclusion

Tendinopathy remains a significant cause of morbidity, with great heterogeneity in anatomical site, stage and phenotype. There is clear unmet need and a clear case for the development and evaluation of new therapies. In addition to disease heterogeneity, the wide range of regenerative and orthobiologic approaches make the interpretation of clinical studies challenging, despite positive reported outcomes. Moving forward, the enthusiasm for new treatments from surgeons, patients, and researchers, together with the current opportunities in new therapeutics, will drive development. A greater stratification of patient and disease with improved targeting of therapy, together with appropriately designed and conducted clinical trials, will build up the clinical evidence for stratified and ultimately personalised interventions. ■

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