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Review Article

Translational science in chronic tendinopathies

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ABSTRACT

Chronic tendinopathies involve majority of patients in clinical practice of orthopaedic surgeons and sports physicians. Translational medicine confers an emerging medical advance efficiently towards the clinician directly from scientists which may be used as a targeted therapy. The main objective of translational research from "bench to bedside" is to test novel inventions in humans. Our purpose in this article to understand the translational medicine approach for chronic tendinopathies in clinical aspects. Translational research in chronic tendinopathies is required certainly due to plenty of reasons. Newer advances and targeted approach to these tendon disorders may curtail the further degenerative process. It aids in earlier diagnosis and prevention of morbidity, early occupancy of occupational activity, lack of economical as well as recreational failure. Pre-disease level activity is ultimate goal of any therapy. Tendon pathophysiology is constantly evolving researched topic in both biochemical as well as molecular aspect. The basic fundamental understanding of complex process of tendon healing and regeneration is necessary for formulating a newer guideline. The cornerstone of treatment of tendinopathies is still non-operative management. Physical therapy, better pain control, NSAIDS are still primary choice for these conditions. Various biological therapy whenever used one should combined them with other appropriate options to obtain an optimum outcome.

Keywords: Tendinopathies, Translational sciences, Tendonitis

INTRODUCTION

Chronic tendinopathies involve majority of patients in clinical practice of orthopaedic surgeons and sports physicians. The burdens of these problems to a society adversely affect the social, economic, occupational, recreational and physical aspect of patients. Majority of these populations are athletes, elderly age group and acute traumatic victims in young patients. The term 'tendinopathy' refers to a pathological condition of a tendon with a complaint of pain and swelling.[1] Management of tendinopathies are not straight forward policy, in addition to that recovery to such conditions is usually a slow process. Various literature suggested that most conditions had a degenerative tendon without having acute inflammation with collagen and myxoid degeneration with increment of ground substances.[2,3] This indicates lacking in self repair process which ultimately directs the newer advances as well as need for future research in regenerative science at a cellular and molecular level which renders the implication of newer enhanced targeted approach for tendinopathies. According to the European Society for Translational Medicine (EUSTM) consists of three pillars: the scientist at his or her bench; the clinician at the bedside; and the community at large. The interaction between the three pillars is bidirectional ("bench to bedside" and "bedside to bench to bedside"). The main objective of translational research from "bench to bedside" is to test novel inventions in humans.

The role of translational sciences in chronic tendinopathies are bleak till last decades but with promising research towards basic sciences may expands the horizon of treatment and clinical implications. Translational medicine confers an emerging medical advances efficiently towards the clinician directly from scientists which may used as a targeted therapy. It is a lesser known entity among reputed clinicians. Our purpose in this article to deliver the translational medicine approach for chronic tendinopathies in clinical aspects. This fulfils the basic objectives of translational science to promote further medical and surgical care with ease. We conducted search in electronic database of google scholar, PubMed, Embase, web of science, Elsevier and science direct with reviews till October 2020. After obtaining search we narrowed our search for articles in terms of getting a literature specifically mentioned about translational medicine, translational sciences, chronic tendinopathies. Methodological quality assessment and analysis were done in order to obtain relevant representation that best suited to our objectives for this article.

30% consultations to primary physician are related to tendinopathies out of total 20% of musculoskeletal visits which representing highly prevalent problem in musculoskeletal medicine for Chronic tendinopathies.[4] There are several factors which contributed to tendinopathies such as: repetitive stress injury, chronic overuse, prolong loading of tendons without rest, acute trauma. Lack of common terminology usage sometimes creates a confusion e.g. tendinitis an old terminology used as its implies an underlying inflammation. Majority of research has already shown that there has been a little or none biochemical or molecular evidence of inflammation in chronic tendinopathies. Cook and Purdam (2009) established the continuum theory for pathogenesis of tendinopathy from asymptomatic tendons to tendon injuries claiming that tendon pathogenesis is a continuum, not an absolute.[5] This concept provides the heterogeneous staging of tendon pathology and suggests that in response to an acute injury or micro trauma, tendons in the progress of pathogenesis undergo a cascade of three phases from normal tendons to tendon tear and rupture.

These phases are as follows: 1) early reactive tendinopathy (non-inflammatory proliferative response in cells and matrix) in response to acute overload or trauma; 2) failed healing response and disrepair of the ECM and finally; 3) terminal degeneration and dysregulation of healing resulting in irreversible stage of pathology showing major structural and compositional changes, cell death, tissue breakdown and loss of function with predisposition of the tendon to further injury and rupture.[5] The multifactorial etiology, epidemiology and pathogenesis of tendinopathies depicted in Figure 1. It also illustrates step wise development of disease and its various steps.There are three main major contributors to tendon pathogenesis: Via matrix – mechanical over activity; Via exogenous cell – new vessel proliferation and Via endogenous cell – cell tissue and aging.[6]

Progression or remission depends always upon patients health, level of activity, administration of treatment.[5,6]

Inflammation in tendinopathies- Many literatures showed an absence of overt inflammation in chronic tendon disorders.[7] Schubert et al noticed the presence of T and B lymphocytes in painful Achilles tendinosis.[8] Moreover, they also found granulocytes in ruptured tendons. Presence of molecular inflammatory markers such as cyclooxygenase-2 (COX-2), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-21 (IL-21), transforming growth factor-b (TGF-b), substance P, and prostaglandin E2 (PGE2) have been observed in various studies conducted for tendinopathies.[8-12] Further laboratory studies are required to determine the direct role of inflammatory markers in tendinopathies. In the pathogenesis of tendinopathy, inflammation and degeneration may not be two separate processes, as these usually interact with each other.

Based on considering an inflammatory as well as degenerative process, routine use of widely available anti-inflammatory therapy in chronic tendinopathies is still debatable entity. Most literature shows anti-inflammatory treatment has short term benefits only and the long-term use of the same may harm the healing process. Poulsen et al noted that corticosteroids induce senescence in tenocytes may be the cause of the detrimental long-term side-effects of it on tendon.[13] The nuclear factor kB (NFkB) signaling pathway plays a pivotal role in normal physiologic process in tendinopathies, in addition to that signaling pathway can be inhibited by small molecule drugs such as resveratrol or curcumin.[14,15] Shakibaei et al showed that in human tenocytes, resveratrol can suppress IL-1 induced activation of the NF-kB pathway, enhancing the production of collagen, tenomodulin and scleraxis expression and inhibiting the expression of genes associated with inflammation and apoptosis.Hu et al,in their study it was shown that the activation of NF-kB signalling pathway can induce the activation of the HIF-2a pathway.[16] Digoxin can inhibit the formation of ectopic ossification in rat tendons and promote the expression of scleraxis (SCX) and tendon repair by regulating the HIF-2a pathway.[16] Regenerative aspects of tendinopathies: Most of the patients present at a very late stage to physician where there is a lack of inflammation and lack of regenerative capacity to tendon. This implies that anti-inflammatory treatment may not completely restore the normal biology of diseased tendon. In the treatment of tendinopathy, there are a number of different strategies to promote tendon regeneration, which focus mainly on three aspects: growth factors, cells and biomaterials. Role of growth factors- During the early healing process of tendons, there are upregulating expression of various growth factors such as basic fibroblast growth factor (bFGF), insulin-like growth factors-1 (IGF-1), platelet-derived growth factor (PDGF), transforming growth factor-b (TGFb) and VEGF which all have pivotal role in a healing process.[17,18] Action and mechanism of growth factors: (A) improvement of local biological condition and

regeneration of different types of tissues; (B) tissue healing regulated by complex processes using growth factors and cytokines; (C) the exogenous introduction of these growth factors may enhance tissue healing even in compromised situations.

Platelet rich plasma and its subtypes have attracted many researchers as well as clinician for its use in chronic tendinopathies since last decade. Its composition is complex and includes a large number of growth factors and proteins. A high-quality randomized controlled trial recently demonstrated that autologous PRP injections have better cure rates and pain scores than cortisone injections for up to 2 years after treatment.[19]

Yan et al studied the influence of leucocytes on PRP-mediated tissue healing, and our study found that leucocyte-poor PRP improved tendon healing with better histological results, which may be a better option for the clinical treatment of tendinopathy when compared to leucocyte-rich PRP.[20] Moreover, PRP also used as an augmentation to surgical repair with promising results.Platelet-rich fibrin (PRF) is the only autologous blood product that releases growth factors and has scaffolding properties. PRF, which is a second-generation platelet concentration, is becoming popular nowadays in orthopaedic surgery.

Role of stem cell therapy is that it may exhert a beneficial effect on chronic tendinopathies. These stem cells types are bone mesenchymal stem cells (BMSCs), TSPCs (tendon stem/progenitor cells), adipose derived mesenchymal stem cells (ADMSCs), embryonic stem cells (ESCs). These cell types creates a favorable molecular environment for tendon healing. Two published studies showed rotator cuff repair with BMSCs injection had lesser numbers of tear and wear with clinical significance.[21,22] Besides, TSPCs are a unique cell population that has both tendon specific and stem cell specific characteristics. TSPCs can maintain the homoeostasis of tendon tissue and can also help to repair the damaged tendon. Lee et al in their pilot study for the treatment of lateral epicondylitis with allogenic adipose derived mesenchymal stem cells noticed statistically significant positive outcomes.[23] In order to find superior treatment protocol, higher level research along with more sophisticated trials are required to establish efficient therapy for tendinopathies.

Role of tissue engineering is that biomaterials are backbone of tendon tissue engineering. Various types of biomaterials provide primary scaffolds where growth factors intervene and healing may be obtained. Collagen, silk, hyaluronic acid, alginate and decellularised tendon xenografts are all natural biomaterials. PRF (Platelet rich fibrin) is one of the acquired yet natural biomaterials used for chronic tendinopathies with promising results. Shen et al fabricated a bioactive knitted silk collagen sponge scaffold which can release stromal cell-derived factor 1a (SDF-1a), enhancing the number of local fibroblast-like cells and inhibiting the accumulation of immunocytes, which enhanced repair of injured tendon.[24]

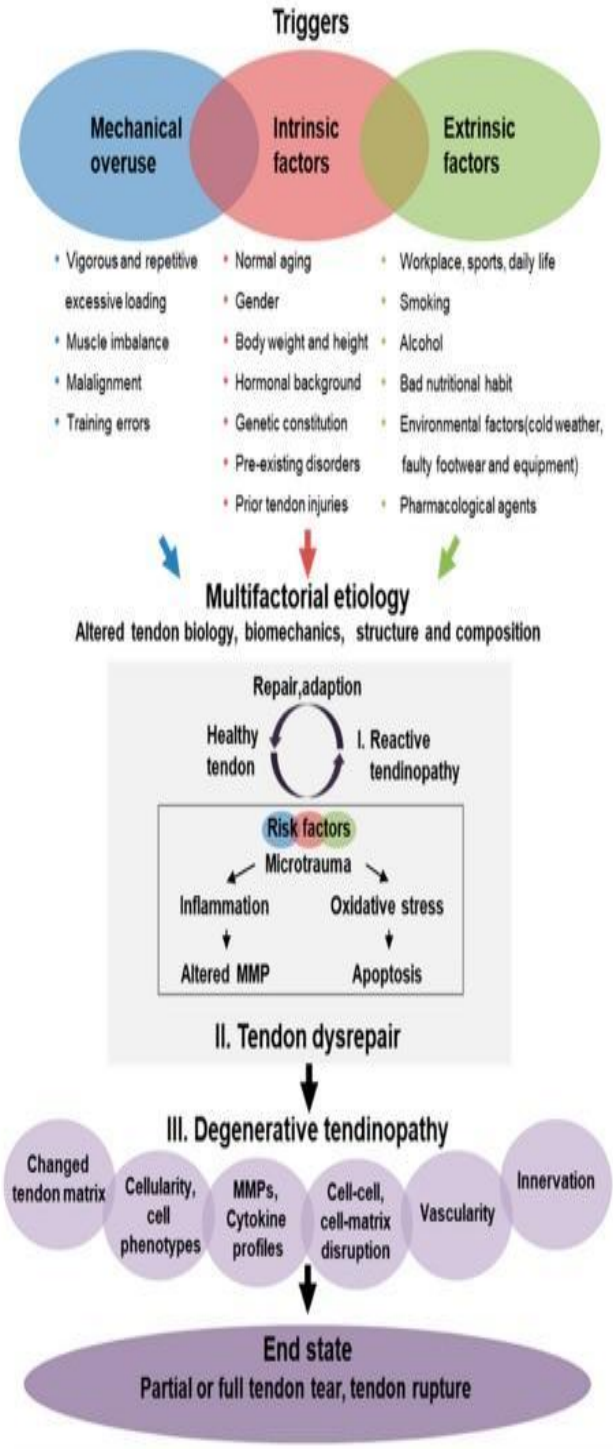

Figure 1: Etiology, epidemiology and pathogenesis of tendinopathies.

DISCUSSION

Management of chronic tendinopathies are challenging. Routine mainstay of tendinopathies is conservative treatment with anti-inflammatory drugs, activity

modification, physiotherapy and pain relief. Due to its multifactorial involvement many patients don't have effective outcome at the end of management. To counteract this problem, we should tailored the patient's condition individually and targeted therapy alongside with newer evidence based approach should be considered. The traditional physical therapy along with ultrasound, phonophoresis and ionophoresis usually yields good results when there isn't underlying major structural abnormalities in tendon.[25] Routine use of corticosteroids and nsaids is now a days controversial and ultimately hampers the healing and many a times due to repeated corticosteroids injection both structural and functional irreversible failure occurs. We need to implement a treatment where symptoms actually heal and haven't masked by treatments. Conservative treatments include ultrasound, shock wave therapy, eccentric exercises and low intensity laser treatments.[26] Combined therapy like regenerative therapy with anti-inflammatory therapy may be required to achieve a better results in the field of tendinopathy. Conservative management is less effective when end stage tendon rupture or advanced degeneration of tendon has already been progressed. Degenerative process of tendons has been well understood by molecular and biochemical advances in last few years. Platelet rich plasma (PRP) and its various subtypes showed some promising results in various chronic tendinopathies such as lateral epicondylitis, roatator cuff injury, plantar fasciitis, patellar tendinopathy and Achilles tendinopathy. Though supremacy of one method over other is still widely debatable issue due to lack evidence and lack of consensus to use them. Conflicting evidence between various studies for same treatment approach does not confer general agreement for treatment protocol for particular tendinopathy. To overcome this obstacle, we should formulate better research trials with larger number of samples and similar inclusion and exclusion criterias.

A newer emerging cell based treatment for chronic tendinopathies is autologus tenocyte implantation where patient's own tenocytes are extracted from healthy patellar tendon biopsy and processed and delivered to defective site via usg guided injection for healing.[27] a new strategy that is being experimentally and pre-clinically explored is tendon tissue engineering, which relies on the application of effective cells injected directly to the site of tendon lesion in order to speed up the restorative process.[28] one third of all patients suffering from chronic tendinopathies don't improve with conservative approach.[29]the surgical goal of these condition is to remove pathology , to achieve induced healing by surgical intervention, to augment the healing process by substituting the tendon with graft and/or biological substances. Percutaneous longitudinal tenotomy usually induced healing process, promotes regeneration in multiple stab wounds site. Recently more advanced percutaneous ultrasonic microtenotomy procedure is able to debride pathologic tissue through a needle-like device placed within the tendon. In a case series of 20 patients with recalcitrant lateral epicondylitis, percutaneous ultrasonic microtenotomy demonstrated improvement in pain and function in 95% of patients treated at one year.[30] Translational research in chronic tendinopathies is required certainly due to plenty of reasons. Newer advances and targeted approach to these tendon disorders may curtail the further degenerative process. It aids in earlier diagnosis and prevention of morbidity, early occupancy of occupational activity, lack of economical as well as recreational failure. Pre-disease level activity is ultimate goal of any therapy. Current guidelines are lacking in agreement for any single guidelines for tendinopathies. Moreover, there aren't any clearly defined ideal treatment protocol. Tendon pathophysiology is constantly evolving researched topic in both biochemical as well as molecular aspect. Clinical implications of such emerging techniques and treatments where "bench to bedside" and "bedside to bench" motto of translational medicine should be fastened in order to achieve a newer approach.

CONCLUSION

The basic fundamental understanding of complex process of tendon healing and regeneration is necessary for formulating a newer guideline. This may include both molecular as well as cellular mechanism which controls and counteracts tendon related pathologic process. Strategies where improved long-term clinical management should be obtained by well-designed future studies, targeted-tendon-specific treatments, more sophisticated multidisplinary research team involved both clinicians and tendon scientist. The cornerstone of treatment of tendinopathies is still non-operative management. Physical therapy, better pain control, NSAIDS are still primary choice for these conditions. Various biological therapy whenever used one should combined them with other appropriate options to obtain an optimum outcome. Future of chronic tendinopathies underlies somewhere in recent researches where it's still to be determined to expand the widest horizon.

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