Review

New directions for the treatment of tendinopathies

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Tendinopathies are among the leading causes of Nova Scotia's high rate of disability and the incidence of tendinopathy is increasing in developed nations with aging populations. The considerable impact of tendinopathies may stem from a shortfall of effective treatments. Presently, even the most successful medical interventions cannot fully restore the properties of damaged tendons. This gap signals a need for novel treatments with the potential to improve tissue regeneration. Increased research into treatments involving (i) transcutaneous nitric oxide, (ii) sclerotherapy, (iii) extracorporeal shock wave therapy, (iv) the administration of growth factors, (v) stem cell therapy, and (vi) biomaterials could help reduce individual suffering, strengthen Nova Scotia's workforce, and decrease the portion of the population relying on limited provincial disability payouts and stipends for disabled persons.

Disability in Nova Scotia

Nova Scotia has the highest percentage of individuals living with disabilities of any province or territory in Canada.[1] In fact, over 30% of Nova Scotians aged 15 years or older lived with at least one disability in 2017 (nearly 250,000 people).[2] This considerable incidence of disability continues to be of detriment to both afflicted Nova Scotians and the province's economy.[3-5] Despite this alarming statistic, there are minimal accommodations for individuals with disabilities in Nova Scotia.[6-7] The province spent $542 per capita on provincial 'Sickness & Disability' funding in 2017.[8] In comparison, Saskatchewan, with a disability rate nearly 25% lower than that of Nova Scotia, spent $1379.[8] This disparity is also reflected in stipends for persons with disabilities; annual disability support in Nova Scotia was $10,264 in 2017 – $2,727 lower than the national average of $12,991.[9] In Ontario, this support was $14,682 and in Alberta it was $19,705.[9] Taken together, Nova Scotia's high incidence of disability and limited available financial support for persons with disabilities stress the importance of adopting novel medical interventions for the treatment of commonly disabling injuries and diseases.

Musculoskeletal Injuries and Tendinopathies

Musculoskeletal injuries have been among the leading causes of Nova Scotia's high rate of disability.[5, 10, 11] The 2017 census revealed that 10.1% of Canadian adults (2.3 million people) had experienced a repetitive strain injury serious enough to limit daily function that year.[12] Moreover, repetitive strain injuries originating from labour-intensive work continue to be the single greatest contributor of working-age disabilities in Canada.[5, 10, 11] In Nova Scotia, repetitive strain injuries and other musculoskeletal injuries accounted for 63% of all lost time claims in 2018.[3, 5, 13] These claims resulted in a mean time off work of 178 days with inability to work occasionally being indefinite in certain labour-intensive professions.[5, 14] As a result, musculoskeletal disorders increase workers' compensation payouts, amplify unrealized economic production, and bring additional costs associated with worker overtime, replacement, and training.[5,13,15–17] Altogether, cost to the Nova Scotian economy is estimated to be at least $100 million annually.[13] In reality, European data suggest the true cost might be ten-fold that amount.[18]

Among the most common repetitive strain injuries are 'tendinopathies'; defined as tendon-related disorders resulting in pain or impaired function.[19,20] Tendinopathies afflict a quarter of adults and comprise half of all musculoskeletal injuries.[3,18,21,22] They are most common in active individuals with high-level runners at over 50% risk of developing pathology to their Achilles tendons during their careers.[16,19,23] Tendon pathology also gives rise to both pain-related and mobility disabilities which are the first (19.8%) and third (13.3%) most common disability types in Nova Scotia, respectively.[1,19,20] This appreciable impact may result from a shortfall of effective treatments for tendinopathy.[24] At present, even the most successful medical interventions cannot fully restore the mechanical properties of damaged tendons.[25]

The lack of good therapeutic options for regaining tendon function has been made more glaring by the increasing incidence of tendinopathy in developed nations with aging

populations.[7,18–20,26] This increasing incidence also extends to Canadian youth – with adolescent basketball players at 23.3% risk of developing patellar or Achilles tendinopathy each playing season.[27] Thus, the time has come to consider novel treatments with the potential to improve the morbidity associated with tendinopathy.

Common Treatments for Tendinopathy

The treatment of tendinopathy has traditionally involved (i) physical therapy, (ii) injection of corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs), and (iii) surgery.[28–31] However, these interventions often result in suboptimal patient outcomes. First, physical therapy with an emphasis on eccentric exercise (involving the lengthening of the affected tendon) has long been considered one of the most effective treatments for tendinopathy;[28,32] but its success relies heavily on patient motivation and thus may be less successful in patients without a substantial athletic history.[31,33] There is also little evidence that corticosteroid injection or NSAIDs administration assist in mediating chronic tendinopathy.[29,30,34,35] In fact, prolonged corticosteroid injection has been associated with tendon atrophy and even spontaneous tendon rupture.[36,37] Finally, reviews of surgical interventions cite that over 30% of patients continue to experience unsatisfactory function in the years following reparative tendon debridement;[38–40] though this figure appears to be improving.[34,41] These existing treatment gaps reinforce the need to explore new means of restoring tendon function.

Future Directions of Tendinopathy Treatment

Transcutaneous nitric oxide

A treatment that has gained momentum in recent years is the transcutaneous release of nitric oxide from glyceryl trinitrate patches which has traditionally been used in the treatment of heart disease.[42,43] Nitric oxide is naturally produced in the event of tendon injury via the upregulation of the nitric oxide synthase family of enzymes.[44,45] An increased nitric oxide level can lead to: (i) increased apoptosis of inflammatory cells, (ii) enhanced angiogenesis and vasodilation, and (iii) amplified tenocyte and collagen proliferation.[29,42,44–47] In this way, increasing local nitric oxide concentration upon tendon injury could play a role in both pain reduction and tendon healing[31,35] – a theory reinforced by multiple studies.[48,49] Indeed, patients suffering from Achilles tendinopathy treated with glyceryl trinitrate patches exhibit greater improvements in tendon power, function, and associated pain than controls.[49] Moreover, 79% of treated patients became asymptomatic at six months compared to 49% of the control group.[49] However, promising results such as these remain contested by skepticism arising from the results of studies showing little or no benefit of glyceryl trinitrate patches over other standard nonoperative treatments.[50,51] Because of this, the widespread adoption of transcutaneous nitric oxide in tendinopathy awaits further clinical assessment.

Sclerotherapy

Another promising intervention is sclerotherapy via polidocanol injection.[52,53] Pathologic regions of tendon tend to exhibit increased vascularization (or proliferations of small blood vessels).[35] Sclerotherapy seeks to decrease tendinopathic pain by obliterating innervation associated with neovascularization.[30,31,35] In addition, sclerosing agents also induce inflammatory responses and thus assist in proliferating tenocytes (tendon fibroblasts) and increasing collagen synthesis.[30,35,53] Two reviews recently supported the use of sclerotherapy in treating chronic Achilles and patellar tendinopathies.[52,53] However, both reviews called for increased research with larger volume studies.[52,53] Moreover, uncertainties persist regarding the potential correlation between the manipulation of neovascularization and the perception of pain.[54,55] Therefore, the rationale behind sclerotherapy hinges on the need for an increased understanding of basic science and subsequent clinical research.

Extracorporeal shock wave therapy

Extracorporeal shock wave therapy (ESWT) was originally developed for the treatment of kidney stones by outputting a series of shock waves with peak pressures approximately 1,000 times that of ultrasound waves.[35,56,57] While tendon function and pain have been found to improve following ESWT treatment[58–60] (though controversy regarding its effectiveness exists[61]), both the mechanism of action and ideal method of application of ESWT remain unclear.[28,35,62] Some suggest that ESWT may be beneficial in its mimicry of mechanical stimulation;[28,60] here, ESWT might assist in promoting the catabolic processes associated with the removal of damaged tendon.[63,64] Alternatively, ESWT has also been proposed to: (i) induce tenocyte proliferation, (ii) degenerate nerve fibers, and (iii) increase the expression of lubricin (a protein that assists in tendon gliding) alongside several growth factors such as transforming growth factor beta-1 (TGF-β1) and insulin growth factor-1 (IGF-1).[63,65–69] While these possibilities are exciting, it remains doubtful that ESWT acts by all of these mechanisms. Thus, further investigation into the precise physiological changes induced by ESWT is necessary to clarify its role with respect to tendinopathy treatment.[28,30,62]

The introduction of growth factors

The alleged upregulation of growth factors like TGF-β1 and IGF-1 in ESWT touches on another prospective area of treatment: the deployment of growth factors through injection of platelet-rich plasma (PRP) or autologous blood (read: growth factor therapy).[35,70] Several studies have suggested that exposing pathologic tendon to exogenous growth factors could aid in tendon healing and the monocytes present in PRP or autologous blood offer a means of such exposure.[30,40,70–72] Tendon injury causes an innate upregulation of growth factors with distinct functions, including IGF-1, TGF-β1, and 'vascular endothelial growth factor' (VEGF).[62,73] IGF-1 may promote extracellular reconstruction by stimulating the production and migration of tenocytes,[74,75] TGF-β1 may play a role in collagen production and the regulation of tendon

proteinases,[76,77] and VEGF supports vascular ingrowth to the area of injury for further delivery of additional growth factors.[78] It seems intuitive, then, that supplying the affected tendon with more of these naturally upregulated factors would aid in healing and, promisingly, this has largely been found to be the case.[79,80] However, the efficacy of providing damaged tendon with PRP or autologous blood has been controversial – stemming foremost from a fundamental lack of knowledge of the spatial and temporal roles of individual growth factors in the process of tendon healing.[81,82] Given the high degree of interaction that occurs between growth factors throughout tendon repair, more effective use of growth factor therapy will ultimately involve administering a 'cocktail' of growth factors deployed at strategic time points of healing.[31,62,83] Until advances in basic science allow for this, simply delivering large quantities of several growth factors may only serve to overload a pathologic tendon and interfere with natural healing processes.[70,82]

Stem cell therapy

Another therapy with promise in mediating tendinopathy is the transplantation of bone marrow-derived or adipose-derived stem cells (BMSCs and ASCs, respectively).[84,85] The injection of stem cells into damaged tendon has been proposed to aid in healing by two mechanisms: (i) by increasing the cumulative secretion of growth factors and cytokines that aid in local regenerative and inflammatory responses, and (ii) by increasing the local cell population via the transformation of stem cells themselves into tenocytes.[86–88] However, the true assistance afforded by stem cell injection remains unclear.[28] A considerable number of animal studies have supported the use of stem cells in the treatment of tendinopathy.[89–91] An example of one such study is the rapid infilling of tendon defects seen following the harvest, in vitro expansion, and implantation of BMSCs into damaged horse superficial digital flexor tendon (a proxy for the Achilles).[92] This has also been echoed in early clinical trials: patients with Achilles tendinopathy have been documented to exhibit faster healing when treated with ASCs than PRP.[93] Based on these findings, stem cell therapy may represent a future line of treatment for tendinopathy.[35] However, trials of stem cell therapy in other organs have resulted in severe side effects such as renal failure, blindness, and glioma.[94–96] Therefore, further research into the plausible dangers of relocating autologous stem cells, as well as a better understanding of their mechanism of action, is needed before they can be safely used in tendons.

Implantation of biomaterials

A final emerging area of tendinopathy treatment is the injection or surgical insertion of manufactured biomaterials into sites of tendon injury.[97,98] Compared to autografts and allografts that have long been deployed in reparative tendon surgery, biomaterials laden with growth factors, stem cells, or gene regulators are promising alternatives with the potential for superior efficacy.[31,99–101] The least intrusive of these are injectable materials like hydrogels (water-based 3D polymeric systems) and microspheres (particles with modified surfaces).[97,102] More invasive options include surgically-introduced scaffolds produced using (i) decellularized tendon, (ii) electrospinning, (iii) 3D printing, or (iv) melt electro-writing.[103–106] Natural polymers (such as collagen or silk), synthetic polymers (poly(lactic-co-glycolic) acid polycaprolactone), and biological scaffolds like extracellular matrix materials have all been proposed as candidates for tendon scaffolding.[103] However, the strengths and weaknesses of some of these materials relative to others – like the remarkable mechanical properties but inferior biological activity of synthetic polymers relative to their natural and biological counterparts[99,104,107,108] – have made it challenging to optimize biomaterial interventions. In light of this, recent research has attempted to use various biomaterials in combination.[98] For example, polycaprolactone fibers were used in conjunction with silk fibroin yarns to deploy the strength of the former and tendon-crimp-like structure of the latter.[109] Other research leveraged the combination of the mechanical strength of collagen fibers with the biocompatibility of hydrogels (as in "fiber-reinforced hydrogels").[98,110] Thus, exploring ways to produce a biomaterial well-suited for a particular tendinopathy by adding other biomaterials is a key focus for future research.

Conclusion

Tendinopathies represent an increasing concern for their anticipated role in further elevating Nova Scotia's already high incidence of disability. Promising means of tendinopathy treatment, including transcutaneous nitric oxide, ESWT, and stem cell therapy, will all require substantial research effort before they can be used clinically. Improved treatment of tendinopathy may help reduce individual suffering, strengthen Nova Scotia's workforce, and decrease the portion of the population relying on limited disability benefits.

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