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The multimodal management of patients with tendinopathy: percutaneous electrolysis, nutraceuticals and lifestyle – report from the 2022 I.S.Mu.L.T. Congress

Educational Section

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Abstract

Tendinopathy is not only induced by mechanical loading but is also related to metabolic noxae. Hypoxia, which may be induced by conditions such as diabetes, obesity and sedentary lifestyle, has been shown to play a role in early tendinopathy. Ultrasound-guided galvanic electrolysis reduces inflammation and promotes collagen synthesis and may be combined with supplementation with nutraceuticals for better tendinopathy treatment. This article provides an update of the multimodal approach to the management of tendinopathy as discussed during the 2022 Italian Society of Muscles, Ligaments and Tendons (I.S.Mu.L.T.) Congress. Prior to the meeting, a search was conducted in PubMed/Medline with crossed keywords relative to the subject. The recommendations of the meeting were that long-term management of tendinopathy should be based on the combination of ultrasound-guided galvanic electrolysis with therapeutic exercise in a rehabilitation plan associated with dietary supplementation with nitric oxide, collagen I, methylsulfonylmethane, and vitamins D and C.

Keywords: arginine, methylsulfonylmethane, nitric oxide, polyphenol, tendinopathy, ultrasound-guided galvanic electrolysis.

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Introduction

Tendinopathy affects millions of people in athletic and occupational settings and impacts sports performance, work ability, and everyday activities.[1] Although analgesic treatment may easily control the acute phase, medical assistance for tendinopathy is sought in later phases, and management can require several months in the clinical practice. Treatment has classically been directed at healing the tendon, focusing primarily on symptoms, as the physiopathology of tendinopathy has only been studied in recent years. Indeed, providing aetiological therapy based on the comprehension of the underlying mechanisms of damage has become a possible aim only recently.

The authors discussed current evidence on the physiopathology of tendinopathy and possible therapeutic targets at the 2022 I.S.Mu.L.T. (Italian Society of Muscles, Ligaments and Tendons) Congress. This article reports on their congress presentations, proposing a management plan directed to the treatment of tendinopathy as a manifestation of a systemic impairment by a multimodal approach.

Methods

To prepare presentations for the 2022 I.S.Mu.L.T. Congress, a search was conducted in PubMed/MEDLINE with crossed keywords "tendinopathy", "treatment", "physiopathology", "supplementation", "nitric oxide", "inflammation", "vitamin D", "vitamin C", "methylsulfonylmethane" and "percutaneous electrolysis". Articles in English or with an English abstract were accepted. Reviews, meta-analyses, and preclinical and clinical studies were read and evaluated.

Overall, 1178 articles were found, of which 10 articles discussed vitamin D, 15 discussed vitamin C, 42 discussed nitric oxide (NO), and 24 discussed percutaneous electrolysis. One systematic review on the use of nutraceuticals was retrieved. The articles were selected by authors based on the relevance to the subject of the article and on their clinical experience. Their congress presentations are summarized herein.

Physiopathology of tendinopathy

The physiopathology of tendinopathy was the first subject addressed during the Congress, and recent evidence was discussed. It is well known that tendinopathy may be triggered by exogenous factors, such as shoe type, work posture, shoe interactions with the work surface, endogenous factors such as misaligned or incorrect posture and concomitant diseases. On the contrary, the molecular mechanisms mediating tendon damage are not fully identified. An abnormal level of stimulation likely plays a role in the aetiopathogenesis of tendinopathy.[2] Mechanical loading is considered a major causative factor for tendinopathy.[1] In increased mechanical loading, tissue strain is transferred from the extracellular matrix proteins collagen and fibronectin to tendon cells, and induces cell deformation.[2] Indeed, the characteristics and loading conditions that may cause tendinopathy are still poorly defined, including extent, frequency of stimulation and duration of strain.[1] Repeated movement has been considered responsible for overuse injuries of the tendon, suggesting that mechano-biological overstimulation of tendon cells could induce degenerative processes, initiating inflammatory events and leading to tendinopathy.[1]

However, studies on animal models have shown that even microtrauma may damage tendon matrix fibrils. These then become unable to transmit load to tendon cells, resulting in reduced stimulation of tendon cells, which, in turn, initiate a degenerative process.[2] Whether linked to the overstimulation or under-stimulation of tendon cells, tendinopathy is characterized by increased expression of degenerative enzymes such as matrix metalloproteinases and mediators of apoptosis.[2] Finally, there is no consistent relationship linking pain, function, and structural changes in tendinopathy. Patients usually present with pain and reduced function but structure, as assessed by ultrasound examination, may be maintained even in the acute phase, whilst pain and functional limitation may be absent in the presence of tissue degeneration observed via ultrasound scan.[3] Treatment decisions cannot rely on simple models of the aetiology of tendinopathy, which are based on the primary event in the pathology cascade. Instead, they require a clinical diagnosis that considers the overall health condition because the management of local and systemic issues is necessary.[3,4]

Hypoxia has been shown to play a role in early tendinopathy by inducing tenocyte apoptosis, which results in tendon tissue degeneration up to tendon fracture. In addition, the increased expression of inflammatory mediators due to hypoxia has a matrix regulation activity as the type III collagen component of the matrix, which has a low resistance, is increased.[5] Increased expression of hypoxia markers was found in tissue samples from established tendinopathy. In contrast, the expression of pro-inflammatory cytokines and mediators of apoptosis was increased in human tendon cells exposed to the hypoxic condition.

The role of NO in tendon health

The authors reported on the role of NO in maintaining and restoring tendon health. NO is a free radical signal-transducing agent, synthesized by NO synthases (NOS) with L-arginine as a precursor. NO is a potent mediator of vessel dilation (which regulates tissue blood flow) and neoangiogenesis (mainly involved in tissue repair). The ability of endothelial cells to produce NO through endothelial NOS activity is critical for the regulation of microvessel circulation. It has been observed that NOS activity is reduced in injured tendons and increased in healing tendons.[6] In addition, it has been shown that NO could enhance collagen synthesis in human tendon cells in vitro.[7]

Long-term treatment targets

The objectives of the clinical management of tendinopathy were presented during the congress to describe suitable interventions. Management of tendinopathy relies on interventions first for pain control, followed by recovery of function and loading capacity, and structure repair. Long-term treatment includes the prevention of recurrence by addressing risk factors (such as metabolic diseases or physical activity) and maintaining the tendon structure integrity.

A first step is tendinopathy risk factor identification, both local and systemic, considering the patient from an integrated perspective. Once these are identified, the locomotor system can be observed and evaluated, focusing on the tendon only as a last objective.

Individuals at risk include athletes and those with metabolic diseases. Therefore, both intense physical activity and a sedentary lifestyle should be considered. In addition, hypertension, diabetes, obesity or steroid exposure have been associated with tendinopathy.[8] Patients with diabetes or insulin resistance are at

increased risk of tendinopathy and have poor outcomes of tendon healing.[9]

All these conditions are characterized by vascular damage, resulting in reduced microvasculature. Such evidence suggests that classical rehabilitative treatment of tendinopathy should be associated with treatment aiming to improve hypoxia.[5] In agreement with these data, locally administered NO had a beneficial effect on tendinopathy in clinical trials.[6,10]

A proposed therapeutic strategy

The authors elaborated a therapeutic strategy based on updated evidence and on their clinical experience and presented it during the congress. A therapeutic strategy based on the beneficial effect of NO may be obtained by supplementation with arginine and by induction of NOS. This latter mechanism is activated by polyphenols, which induce NO, resulting in vessel wall protection and improvement of vascular function.[11] The dietary supplementation with arginine and polyphenols, which may increase the bioavailability of NO, seems beneficial in the long-term treatment of tendinopathy, as shown by Notarnicola et al.[12] The improvement of tendon metabolism could enhance the efficiency of rehabilitative interventions on the tendon structure.

Ultrasound-guided galvanic electrolysis is a technique used in the rehabilitative management of tendinopathy.[13,14] A galvanic electric current is released in the tendon by a needle, inducing an electrochemical reaction in degenerative tissues and resulting in inflammation. This process facilitates macrophage phagocytic activity and scavenging of tissue debris, followed by neoangiogenesis.[15] The treatment is repeated to induce a first inflammatory phase, where tissue debris is removed, and a proliferation phase, where collagen synthesis is promoted, and may improve the outcomes of therapeutic exercise.

This technique may be combined with appropriate supplementation to promote vasodilation and control inflammation in the acute phase of tendinopathy and increase vascular flow in the proliferation phase. Administration of arginine and polyphenols may activate these mechanisms by the NO pathway.

The use of a supplement containing L-arginine α-ketoglutarate, polyphenols, type I collagen, methylsulfonylmethane, type I collagen and bromelain, for 3 months, decreased post-operative pain after cuff repair, and this effect could facilitate the post-operative rehabilitation programme.[16]

According to the authors, from an integrated perspective, supplementation in individuals with tendinopathy should involve oral intake of nutraceutical products such as vitamin D, nitrates and methylsulfonylmethane, which would be beneficial for the health of the entire motor system, as bone and muscle health cannot be dismissed.

In particular, in an animal model of an injured tendon–bone interface, vitamin D deficiency negatively affected the early repair phase in local bone formation and collagen fibre organization at 4 weeks from trauma.[17] In addition, supplementation restores protein synthesis in the muscle of vitamin D-deficient animals.[18] High-dose vitamin C supplementation accelerates tendon healing.[19]

As previously mentioned, inflammatory cytokine production plays a role in the physiopathology of tendinopathy, and control of the inflammatory phase may be beneficial. To this aim, the administration high dosages of methylsulfonylmethane, which has been demonstrated to dampen the release of inflammatory molecules in response to exercise and to influence some markers of exercise recovery, might be helpful.[20,21] Some studies demonstrated that nitrates may be beneficial for muscle activity, which suggests a possible role in the healing phase of tendinopathy. Indeed, a recent systematic review with metanalysis concluded that acute or chronic dietary nitrates intake significantly increase maximal muscle power in humans.[22] Acute nitrates supplementation by administration of beetroot increased power output during concentric and eccentric muscle contractions.[23] Finally, dietary nitrates supplementation attenuated the development of muscle fatigue by reducing the exercise-induced impairments in contractile muscle function and lowered the perception of both effort and leg muscle pain during exercise.[24] To this aim, the supplementation of nitrates in combination with high doses of L-arginine α-ketoglutarate, the precursor of NO, triggers blood vessel dilation and increases blood flow in skeletal muscle.[16]

Conclusion

In conclusion, based on the presented information, tendinopathy is induced not only by mechanical loading but is also related to metabolic noxae such as hypoxia, inflammation, apoptosis, and hormonal effects. Both athletes and individuals with diabetes have an increased risk of tendon pathology.

A correct and complete diagnosis is necessary to choose an appropriate treatment, assessing the concomitance with diabetes. In addition, the long-term management of tendinopathy should be based on the combination of ultrasound-guided galvanic electrolysis with therapeutic

exercise in a rehabilitation plan associated with dietary supplementation, aiming at improving blood flow, controlling inflammation, and providing muscle and bone with vitamins D and C along with the necessary amount of collagen. This could be achieved by once-daily oral administration of a preparation containing high dosages of L-arginine α-ketoglutarate (2000 mg) and patented methylsulfonylmethane (OptiMSM®, 3000 mg), high-concentration all-natural nitrates (TruBeet®, 500 mg), in addition to polyphenols from Vitis Vinifera (vinitrox), collagen I, vitamin D and high-dose (1000 mg) vitamin C. This long-term treatment could efficiently improve the effects of intratissue percutaneous electrolysis and prepare the patient for physical rehabilitation.

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