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MYOFASCIAL PAIN (R GERWIN, SECTION EDITOR)

Clinical Relevance of Fascial Tissue and Dysfunctions

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Abstract Fascia is composed of collagenous connective tissue surrounding and interpenetrating skeletal muscle, joints, organs, nerves, and vascular beds. Fascial tissue forms a whole-body, continuous three-dimensional viscoelastic matrix of structural support. The classical concept of its mere passive role in force transmission has recently been disproven. Fascial tissue contains contractile elements enabling a modulating role in force generation and also mechanosensory fine-tuning. This hypothesis is supported by in vitro studies demonstrating an autonomous contraction of human lumbar fascia and a pharmacological induction of temporary contraction in rat fascial tissue. The ability of spontaneous regulation of fascial stiffness over a time period ranging from minutes to hours contributes more actively to musculoskeletal dynamics. Imbalance of this regulatory mechanism results in increased or decreased myofascial tonus, or diminished neuromuscular coordination, which are key contributors to the pathomechanisms of several musculoskeletal pathologies and pain syndromes. Here, we summarize anatomical and biomechanical properties of fascial tissue with a special focus on fascial dysfunctions and resulting clinical manifestations. Finally, we discuss current and future potential treatment options that can influence clinical manifestations of pain syndromes associated with fascial tissues.

Keywords Myofascial pain · Fascia · Lumbar fascia · Dysfunction

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Introduction

In recent years, fascia has aroused increasing interest for both biomedical scientists and manual body therapists [1]. This is, at least in part, a result of recent developments in tissue imaging and advanced assessment technologies: high-resolution ultrasound to assess the efficacy of manual therapy; in vivo measurement of fascial behavior using myometry or bioelectrical impedance; and digital analysis of the fascial tissue throughout the body [2–4]. International research networks were founded, which now hold regular meetings (e.g., fasciaresearchsociety.org). At the first fascia research conference (Boston, MA, USA), definitions of fascial tissue were determined, which comprise connective tissue sheets such as aponeuroses; joint and organ capsules; and also muscular connective tissue. The components are interconnected throughout the whole body, making up a three-dimensional architecture that is a multilayer system of interconnected sheets [2, 5, 6•].

Anatomy of Human Fascial Tissue

Muscular fascia is composed of three structures: superficial fascia, more dense deep fascia; and muscle-related layers (epimysium, perimysium, and endomysium) [7]. The superficial fascia is a macroscopically well organized membranous fibroelastic tissue that is, with the exception of the face, the soles of the feet and the palms of the hands, found ubiquitously throughout the human body [5]. Microscopically, its structure has been described as being like a tightly packed honeycomb [8]. The deep fascia is a membrane that extends throughout the whole body and is kept under basal tension via numerous muscular expansions [6•]. Based on this anatomical composition, fascial expansions transmit the tension generated by muscle contraction to the neighboring areas, resulting in stimulation of the proprioceptors within this area [9]. Histologically, the deep fascia is formed of a single layer of undulated collagen fibers intermixed with elastin fibers, and independent of the underlying muscle, separated by the epimysium and a layer of loose connective tissue [6•].

Biomechanical Properties of Fascial Tissue

Fascial tissue exhibits a regulative function during mechanical force transmission, bypassing mechanical forces via lateral cross-links, buffering energy, and strengthening movements in a way similar to a servomechanism steering a car. Recently, functional ultrasonic investigations of the musculus gastrocnemius and soleus provided exciting findings: contrary to the classical point of view, these muscles operate in an almost isometric manner [10]. The main shortening and elongation is mediated by fascial tissue, which is, moreover, enhanced with movement frequency toward a greater use of the tendon elastic energy at higher frequencies. In particular, the Achilles tendon operates like an elastic spring, which is able to absorb, store, and release kinetic energy. The fascia thoracolumbalis functions as an energy reserve, which is discharged or recharged during every single step. Biomechanical investigations with working women of the African Kikuyu clan revealed that these women are able to carry 70 % of their own body weight on their head, with only minimally increased energy expenditure [10, 11]. The effectiveness of energy storage in fascial tissue is reinforced by several animal examples: gazelles and kangaroos use connective tissue as an elastic spring, utilizing this mechanism in their primary methods of locomotion [12]. A totally different but no less intelligent mechanism is provided by the fascia of the spleen: racehorses are able to store 30 % of their erythrocytes within the spleen, which can be released by contraction of the spleen organ capsule. This autotransfusion results in increased physical capacity owing to an increased capacity to transport oxygen [13]. This mechanism is currently unverified in humans; however, the phenomenon of "stitch" is possibly related to a painful distension of the fascial liver and/or kidney organ capsule: unbalanced compensatory mechanisms during athletic endeavors may cause a precardial venous congestion followed by stasis of the venous vasculature and, owing to the low resistance, particularly within the liver and spleen, finally results in tensional pain of the organ capsule.

Matrix Remodeling in Fascial Tissue

The extracellular matrix (ECM) has been considered to be an amorphous scaffolding that provides long-term mechanical support. However, recent insights have revealed that this matrix is a very dynamic structure that modifies mechanical and viscoelastic properties, decreases stress susceptibility, and may increase load resistance [14]. The skeletal muscle ECM consists of noncollagenous glycoproteins and is reinforced by stiffer fibrous proteins. By building a supramolecular networking system, this matrix can transmit contractile muscle forces while maintaining tissue integrity. The ECM provides intramuscular continuations of neuromuscular tracts in which blood vessel and nerve branches are embedded [14, 15•]. The viscoelasticity of fascial tissue can alter activation of the nerve receptors within fascia: mechanoreceptors respond to surrounding tissue viscoelasticity and participate in their response [16•]. Moreover, molecules of the ECM interact with the sarcolemmal, cytoskeletal, and nuclear elements to maintain skeletal muscle integrity [14]. Growing insights into the importance of the ECM have revealed that defects or deficiencies in these proteins can result in myopathies like Bethlem myopathy or congenital muscular dystrophies [17].

Inflammation, Myofibroblasts, and Fibrosis

Repair of damaged tissue generally begins with a regenerative phase, consisting of inflammation and proliferation of stem cells [18, 19]. Early after injury, innate immune cells invade damaged skeletal muscle areas to phagocytose tissue debris and to release signaling molecules to attract further immune cells (Fig. 1.). There is a complex interaction between fibroblasts and skeletal muscle stem cells (satellite cells). Ablation of fibroblasts in a genetic mouse model has been shown to deplete the satellite cell pool and reduce the size of regenerating muscle fibers [20]. Release of cytokines and chemokines from inflammatory cells contributes to satellite cell and fibroblast activation during the early stages of regeneration [21, 22]. However, chronic inflammation and fibroblast activation, for example during chronic tissue damage and regeneration in muscular dystrophies, attenuates the regenerative capacity of satellite cells [23].

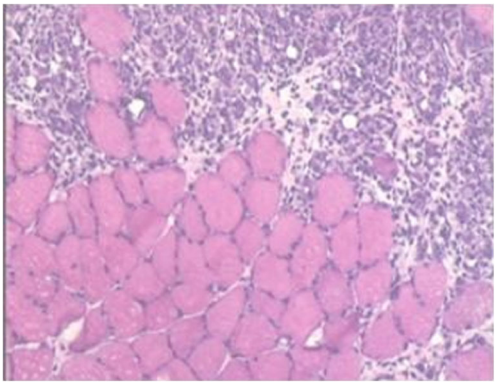

Fig. 1 Hematoxylin/eosin stained rat skeletal muscle cross-section after toxin-induced injury. Mononuclear immune cells (dark blue) invade injured skeletal muscle areas 12 h after injury [18]

Use of nonsteroidal anti-inflammatory medication (NSAIDs) is widespread in the sporting community to reduce pain prior to or after intense or unaccustomed exercise. However, chronic use of NSAIDs has been shown to impact negatively on satellite cell activation and proliferation during recovery from endurance and strength exercise [24, 25]. In contrast to skeletal muscle regeneration, no inflammatory response could be observed after acute exercise in tendinopathic human tendon. Consequently, treatment with NSAIDs had no effects on inflammatory gene expression in tendinopathic Achilles tendon [26].

Chronic inflammation can lead to the development of scar tissue formation (fibrosis). Fibrosis is the leading cause of deaths in the USA, where 45 % of deaths can be attributed to some type of fibroproliferative disease, such as pulmonary fibrosis, systemic sclerosis, liver cirrhosis, cardiovascular disease, progressive kidney disease, and macular degeneration [27]. Fibrosis occurs owing to the excessive production of ECM components such as collagen and fibronectin by contractile myofibroblasts, which are characterized by the expression of α-smooth muscle actin [28, 29]. Myofibroblasts originate from different cellular sources depending on the pathology or physiological situation, including locally residing mesenchymal cells such as fibroblasts and bone marrow-derived fibrocytes [30]. Mechanical stress, as well as the presence of transforming growth factor (TGF)-β1, is essential to convert fibroblasts to myofibroblasts [31]. Contractile activity of myofibroblasts increases in response to extracellular mechanical challenges due to increased calcium oscillation frequencies [32]. Furthermore, cytokines and growth factors released from immune cells during the inflammatory response stimulate the migration of fibroblasts into damaged tissue regions and trigger the phenotypic switch towards myofibroblasts [33]. Mesenchymal cells from the vasculature, such as pericytes and smooth muscle cells, serve as myofibroblast precursors during blood vessel repair and are also involved in the development of systemic sclerosis [34]. In the heart, excessive collagen production by cardiac myofibroblasts contributes to myocardial stiffness, which compromises ventricular function [35]. To date, there are only limited therapeutic options for progressive fibrotic diseases. Use of systemic antifibrotic agents, such as inhibitors of TGF-β1 [36], remains controversial because global inhibition of TGF-β1 could impair tumor suppression and stimulate chronic inflammation. Modern therapeutic approaches to treat fibrosis include antagonism of fibrotic factors in a tissue-specific manner or target molecules that are expressed only in diseased tissues [37].

Increase of Fascial Stiffness

Increased matrix stiffness can lead to, or contribute to, myofascial pain. Most notably, painful contractures are mostly associated with an increase in fascial tissue (Table 1). Global conditions include spastic palsy, for example after stroke; neuromuscular disease; or autoimmune diseases, such as rheumatoid arthritis or scleroderma. Focal increase of fascial stiffness is found in several contractures that are characterized by a dense connective tissue rich of myofibroblasts, which are often associated with past or present inflammatory processes.

Table 1 presents an overview of related pathologies. The following sections highlight only a few of these conditions.

Hypermobility

A lack of tissue stiffness can lead to soft tissue pain. One of the most frequent conditions in this respect is general joint hypermobilty. When associated with symptoms it is referred to as hypermobility syndrome (Table 1). This condition is characterized by an excessive range of joint movement, taking age, sex, and ethnicity into consideration. It is considered a hereditary multisystemic connective tissue disorder. Prevalence in European populations is reported as 10 %; in other ethnic groups it is 25 %. It is more frequent in women, and an association of this condition has been confirmed with fibromyalgia, mitral valve prolapse, and panic disorder [38].

The soft tissue pain associated with this condition tends to be widespread without conforming to anatomical details, and tends to be resistant to even strong analgesics, including opiates. Pain is often aggravated by active movement, and therefore the condition is frequently associated with kinesiophobia. Current therapeutic strategies include exercises for core and joint stabilizing, proprioception enhancement, coupled with pain management training based on cognitive behavioral therapy, as well as with a general fitness program aimed at reversing the inevitable muscle conditioning that results from pain inhibition and kinesiophobia.

Table 1 Comparison of fascial dysfunctions affecting biomechanical tissue properties

	Lack of stiffness	Increase of stiffness	Decreased shearing ability
Local	• Inguinal hernia	• Dupuytren contracture	• Nerve compression syndromes
	• Abdominal hernia	• Frozen shoulder	• Postsurgical abdominal adhesions
	• Lumbar hernia	• Morbus Ledderhose	• Chronic low back pain
		• Hypertrophic scars	
		• Peyronie's disease	
		• Plantar fasciosis	
Global	• Ehlers-Danlos syndrome	• Sclerodermia	
	• Marfan syndrome	• Duchenne dystrophy	
	• Hypermobility syndrome	• Spastic paresis	
		Major organ fibrosis	

Nociception, Neuroplasticity, and Pain Mediators in Fascial Tissue

Sensory feedback of myofascial tissue is critical in directed neuromuscular control of coordination and movement patterns. Functional neurophysiological, as well as histopathological, investigations have suggested that fascial connective tissue is a potential source of pain. Within fascial tissue, so-called "wide dynamic range" neurons were found to predominate, which can detect multiple sensory signals. Electrophysiological investigations have revealed that the impulse activity and the number of spinal cord neurons after stimulation of fascia is very variable. Artificial inflammation of the lumbar fascia causes a significant increase of posterior horn neurons receiving afferent signals from fascial tissue, as well as a significant increase of posterior horn neurons with converged impulsion from different tissues. Finally, the central nervous system is very sensitive to received fascial information caused by pathological changes in the lumbar area of the back [39]. Recently, Schilder et al. [40••] found support in humans for this theory: pain effects evoked by ultrasound-guided bolus injection of hypertonic saline in fascial tissue exceeded those of muscle. Interestingly, pain after fascia injection, was described by the patients in rather extreme terms like "torturous", "exhausting", "and agonizing", which suggests innervation by both A- and C-fiber nociceptors. In contrast, muscle-derived pain was predominantly attributed to sensory qualities like "stinging", "numbness", and "throbbing" [40••]. Apart from biogenic amines, interleukins, growth factors, and additions humoral factors, Tesarz et al. [41] also detected substance P and calcitonin gene-related peptide-dependent neurons in fascial tissue. Both substances are known mediators in chronic pain [41].

Collagen Tissue as a Source of Pain

Stiffening of connective tissue accompanies several pain syndromes, which include exercise-induced lower leg compartment syndrome, the so-called runners' knee, tennis/golfer elbow, frozen shoulder, and fasciitis. Histological investigations show accumulations of fibroblasts or contractile myofibroblasts. Whether these cells are contributors to the pathogenesis of connective tissue induced contractures is currently still under investigation. Moreover, recent data have revealed that fascial epimysium is a central participant in the pathogenesis of the sport induced "muscle ache" [42].

Unspecific back pain was also suggested to be mediated, at least in part, by fascial structures, especially the thoracolumbar fascia. This fascia receives a large part of the mechanical force transmission during lumbar flexion and is rich in nociceptive nerve endings [41]. Cracks in the thoracolumbar fascia, muscle hernias, microlesions, and mechanical irritations can result in malfunctions and painful contractures. Interestingly, a tendency towards an increase in thickness (of about 25 %) is found in men with chronic back pain. Additionally, a reduction in shear motion (i.e., sliding ability during passive lumbar flexion) of this fascial structure in relation to the underlying musculature has been documented for both sexes [43]. Injection of nerve growth factor (NGF) within the thoracolumbar fascia caused hyperalgesia. This finding may open a new and promising method of treatment for low back pain the inhibition of NGF using monoclonal antibody (Tanezumab) caused analgesic effects in those suffering from back pain syndromes [39].

These cells are known to be either contractile smooth muscle cells or fibroblast with smooth muscle like features, for example myofibroblasts [44]. In vitro investigation revealed contractile properties of myofibroblasts, which are regulated by inactivation of the myosin light chain phosphorylation via the Rho-associated kinase ROCK, leading to inactivation of myosin light chain phosphatase, and, finally, continued contraction [45, 46]. In vivo experimentation using rat fascial tissue confirmed these results: suspended thin strips in a superfusion system yielded clear and reversible tissue contractions in response to pharmacological drugs [47]. Isometric stretching of strips of human lumbar fascia tissue (1.5 mm× 1.0 mm×30 mm) resulted in a maximal measured force

increase of up to 1.5 N. Application of this ratio to whole fascial tissue sheets revealed substantial force in active contractions within a range at which a lumbar paraspinal compartment syndrome could be triggered [48]. In contrast, decreased fascial tonus can result in spinal segmental instability, and a total loss of fascial tone can contribute to hypermobility, as frequently occurs during pregnancy [49, 50].

Recently, the critical role of connective tissue was proven regarding the understanding and treatment of spastic pareses in children: apart from targeting the main pathological mechanism, for example the neuromuscular interaction, investigations revealed that the clinical behavior of these children is often more crucially influenced by additional changes observed in muscular connective tissue. The recognition of increased epimuscular force transmission to antagonistic muscles (via increased endomysial and perimysial cross-links) has now lead to encouraging surgical advances in this field [15•, 51, 52].

Frozen Shoulder

One of the most common syndromes is frozen shoulder. The condition expresses as symptoms of shoulder pain and discomfort that are slow in onset and located around the deltoid insertion. Patients commonly express reduced glenohumeral abduction and external rotation, accompanied by unremarkable radiographic findings. Upon palpation of the glenohumeral joint, tenderness is often felt at this location. The condition mainly affects patients aged 40–60 years, with a female predominance. Prevalence is increased in patients with diabetes, cardiovascular disease, hyper- and hypothyroidism, and Parkinson's disease. In addition, protease inhibitors used for antiretroviral therapy have been associated with the development of this condition. It remains unclear why the contracture limits abduction and external rotation despite a global capsular fibroplasia. Biopsies obtained during surgery have revealed a thickened capsule and coracohumeral ligament. Immunohistochemical examinations have revealed a dense matrix of type III collagen populated with fibroblasts and myofibroblasts in the capsule. In addition, there are varied and sometimes contradictory reports about increased vascularity, fibrosis, hyalinization, vascular villous synovitis, and the presence of mature scar tissue. However, little evidence of an acute inflammatory process is found. Generally, frozen shoulder is a regarded as a self-limiting condition. The pathology then usually progresses through three clinical phases: (1) a painful phase with a gradual onset, usually worse at night and when lying on the affected side, with a duration of 2–9 months; (2) stiffening phase with usually no change in the pain level—the stiffness progresses and may lead to muscle atrophy due to disuse, with a duration of 4–12 months; (3) thawing phase, in which the patient shows a gradual improvement in rage of movement, as well as in the pain aspect, although it may reappear as the stiffness eases (duration of this phase is 5–12 months).

Chronic Neck Pain

A recent ultrasound examination of patients with chronic neck pain revealed that they tend to have a greater fascial thickness at the sternal endings of the sternocleidomastoid, as well as at the lower and upper side of the medial scalene muscle. In particular, a measurement of 0.15 cm (the mean value of two SDs of controls) of the sternocleidomastoid fascia was considered to be a cut-off value, which enables clinicians to make a diagnosis of myofascial pathology—rather than of a primary neuromuscular dysfunction—in a patient with chronic neck pain. The increase in thickness was associated with an accompanying reduction in active, as well as passive, cervical range of motion in the pain group. Taken together—the increase in thickness and the reduced mobility—the authors postulated an increased stiffness of related muscular fasciae.

Following a series of fascial manipulation sessions a significant decrease in the thickness of the fasciae were found accompanied by a reduction in pain, as well as increased range of motion [53••].

Nerve Compression Syndromes

Peripheral nerve compression syndromes can be detected at different locations throughout the human body, which depend, at least in part, on the kind of sport activities.

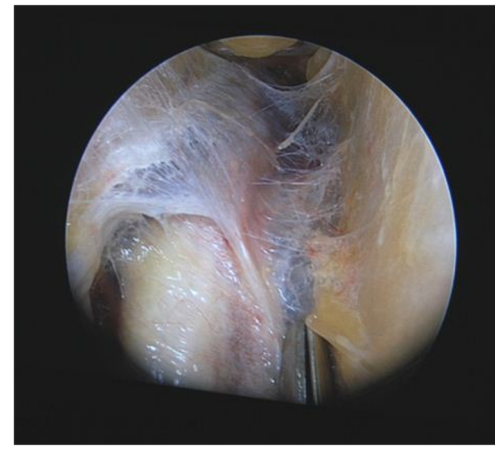

Fig. 2 Nerve entrapment syndrome. The figure shows an endoscopic photograph of the ulnaris nerve in the cubital tunnel distal to the Osborne fascia. Abnormal thickenings of perineural fascial tissue compress the nerve and lead to a long-segment stenosis. Irritation of the nerve leads to a partial or total loss of function characterized by pain, decreased haptic perception and loss of muscle force, and muscle atrophy. Pain is typically referred to the ulnar part of the wrist. However, retrograde transmission of pain predominantly at night-time can mimic a cervical spine stenosis

Nerve compression syndromes are always associated with a fascial pathology. Pressure, traction, and repetitive irritation may trigger relocating disturbances and increased thickness of fascial tissue, which restrict the corresponding nerve. Consequently, the nerves swell at the restriction and the endoneural fluid pressure increases, resulting in an insufficient blood supply of the corresponding nerve segment. Finally, a painful function restriction in the innervated area occurs.

The Osborne fascia between the epicondylus medialis and the olecranon represents an anatomical narrowing that can compress the nervus ulnaris within the cubital channel. This painful compression is treated with the surgical separation of the Osborne fascia. However, recent investigations have revealed that increased fascial thickness might also compress the nerve at regions other than the cubital channel (Fig. 2). This has resulted in the development of a new surgical method that investigates the whole course of the nerve endoscopically. Fascia research has thus increased the success rate of this procedure.

Concluding Clinical Perspectives

In research studies oriented around soft tissue pain, the dominant emphasis has been on the examination of neuromuscular processes. Recent advances in the rapidly evolving field of fascia research suggest that pathological changes in fibrous collagenous connective tissues (fasciae) could additionally play a contributing role in several myofascial pain syndromes. These encompass conditions characterized by altered stiffness of related fascial tissues and/or by a decrease in their sliding ability or shearing motion (see Table 1).

A better understanding of the cellular dynamics involved in fibrosis promises to enrich the range of therapeutically available options. Manual myofascial therapies, as well as specifically targeted fascial movement therapies, may be able to assist in the process of improving matrix remodeling. For example, myofascial abdominal massage has been shown to reduce intra-abdominal adhesions in rats [54•], and in vitro application of a super slow fluid shear motion was able to induce the increased expression of matrix metalloproteinase-1, a potent antifibrotic enzyme [55]. Advances in ultrasound imaging (including sonographic elastography) and in myometry promise to become helpful tools in the assessment of pathological, as well as therapeutically induced, changes in fascial tissue properties associated with many myofascial pain syndromes rats [56, 57].

Compliance with Ethics Guidelines

Conflict of Interest The authors each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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