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Fascia Science and Clinical Applications

Deep fascia as a potential source of pain: A narrative review

Kobi Weiss , Leonid Kalichman *

Department of Physical Therapy, Recanati School for Community Health Professions, Faculty of Health Sciences at Ben-Gurion University of the Negev, Beer-Sheva, Israel

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ABSTRACT

Background: The fascial component of the myofascial pain syndrome and the contribution of the deep fascia to various painful conditions has not been well-described and is still less understood.
Objectives: The aims of this study were to evaluate the possible role of the deep fascia on musculoskeletal pain, focusing on findings from histological and experimental studies; and to assess the nociceptive and associated responses of the deep fascia to experimentally-induced irritation.
Methods: Narrative review of the English scientific literature.
Results and conclusions: Different components of the deep fascia, both in humans and animals are richly innervated, with some differences between body segments. These fascial components usually exhibit dense innervation, encompassing amongst others, nociceptive afferents. The application of different types of stimuli, i.e., electrical, mechanical, and chemical to these fascial components produces long-lasting pain responses. In some cases, the intensity and severity of pain produced by the stimulation of fascia were higher than ones produced by the stimulation of the related muscular tissue. These observations may denote that the deep fascia and its various components could be a source of pain in different pathologies and various pain syndromes.

1. Introduction

Myofascial pain syndrome is widely recognized as a common source of pain in musculoskeletal medicine. Muscle and nerve components of this syndrome, i.e., motor, sensory, and autonomic, have been studied over the years (Eng-Ching, 2007; Shah and Gilliams 2008; Borg-Stein and Simons 2002; Bennett 2007; Giamberardino et al., 2011). The association of myofascial pain with various musculoskeletal morbidities has been demonstrated in numerous studies (Saxena 2015; Fernández-de-las-Peñas 2015; Dor and Kalichman 2017; Shmushkevich and Kalichman 2013; Sergienko and Kalichman 2015; Lisi et al., 2015). In contrast, the fascial component of the myofascial pain and the contribution of the deep fascia to various painful conditions has been less described and still less understood.

Over the years, the definition of the fascia and the fascial system has undergone several significant modifications. The current definition as presented by a position paper from the Fascia Nomenclature Committee of the Fascia Research Society (Stecco et al., 2018) stated: "The fascial system consists of the three-dimensional continuum of soft, collagen-containing, loose and dense fibrous connective tissues that permeate the body. It incorporates elements such as adipose tissue, adventitia, and neurovascular sheaths, aponeuroses, deep and superficial fasciae, epineurium, joint capsules, ligaments, membranes, meninges, myofascial expansions, periosteum, retinacula, septa, tendons, visceral fasciae, and all the intramuscular and intermuscular connective tissues including endo-/peri-/epimysium. The fascial system surrounds, interweaves between, and interpenetrates all organs, muscles, bones, and nerve fibers, endowing the body with a functional structure, and providing an environment that enables all body systems to operate in an integrated manner". This definition should be taken into consideration when reviewing the existing literature, reflecting on the ongoing and dynamic fascial research.

Over the past 20 years and especially since the 2007 1st International Fascial Research Congress in Boston, USA, numerous studies have been performed to determine the role of deep fascial tissue in musculoskeletal pain syndromes. The aim of the present review was to clarify and summarize the current knowledge on this subject focusing on two issues: (1) histological evidence for innervation and the nociceptive potential of various elements of

* Corresponding authorDepartment of Physical Therapy, Recanati School for Community Health Professions, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.
E-mail address: kleonid@bgu.ac.il (L. Kalichman).

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the deep fascia; and (2) the nociceptive and associated responses of the deep fascia to experimentally-induced irritation.

2. Methods

PubMed, Google Scholar, ProQuest, ScienceDirect, and PEDro databases were searched from inception until September 2020 using the following keywords: fascia, deep fascia, pain, nociception, innervation, nerve fibers, and the combinations of these terms. The reference lists of all articles retrieved in full were also searched. The search results were pooled, and duplicates were deleted. The titles and abstracts of all articles were reviewed. Full texts of potentially relevant papers were read, and their reference lists searched for additional relevant articles. Criteria for inclusion were any type of research dealing with the deep fascia as a potential source of pain, published in English. Information from the selected articles was summarized and used for each section contained in this narrative review. The initial search revealed 312 papers. After applying the search criteria, we found 27 fully matched papers. Additional 12 studies were used in the Introduction section to present the topic.

3. Results and discussion

3.1. Innervation

Histological studies focusing on the deep fascia as a potential source of pain have generally reported on the thoracolumbar fascia. Unmyelinated nerve terminals, considered to possess nociceptive potential, have been observed in the thoracolumbar fascia. Wilke et al. (2017) reviewed and analyzed the literature in order to explore the potential role of the thoracolumbar fascia as a source of low back pain, concentrating on histological and experimental findings. The reviewed studies performed on animals and/or humans did not include studies on supraspinous, inter-spinous, or iliolumbar ligaments. These studies identified mechanoreceptors, such as Pacinian corpuscles, Pacinian-like and Golgi-Mazzoni corpuscles, and free nerve endings with a nociceptive capability. The identified nerve endings included nerves that possess the nociceptive capability and contain substance P (i.e., positive for substance P staining) (Hoheisel et al., 2015; Mense and Hoheisel 2016). Nerves with an apparently nociceptive potential, positive for calcitonin gene-related peptide (CGRP), and a marker for presumably nociceptive fibers (Hoheisel et al., 2015; Mense and Hoheisel 2016; Corey et al., 2011; Tesarz et al., 2011; Barry et al., 2015) were also identified.

Simons et al. (2018) corroborated those findings in a subsequent literature review. An interesting finding emerged from Barry et al.'s study (2015) demonstrating that the innervation density in the thoracolumbar fascia was three times higher than in the examined back muscles. On the other hand, in one of the reviewed studies conducted on humans, no terminal nerves were found (Bednar et al., 1995). Two other studies (Benetazzo et al., 2011; Stilwell 1957) reported that the type of nerve endings observed was not characterized nor examined.

In a recent publication, Mense (2019) reported on the sensory functions of the thoracolumbar fascia, mainly based on immune-histological data obtained from rats but also included outcomes from a few samples taken from patients who had undergone a spine operation due to an acute accident. The histological examination visualized nerve fibers with CGRP-positive and substance P-positive endings. These two, as mentioned earlier, are considered a nociception potential. Mense presents an interesting finding that the substance P containing nerve fiber and endings was absent from the middle layer of the thoracolumbar fascia, found mainly in the outer layer and the subcutaneous tissue. This finding was also observed by Mense and Hoheisel (2016) in a previous study. The authors claimed that these results were due to mechanical issues related to the structure and function of the middle layer. Furthermore, histologically, it was observed that the transient receptor potential channel V1 endings were the main receptor molecules in the membrane of nociceptors. In addition to the thoracolumbar fascia, other components of the deep fascial system have been investigated as to their potential as a source of pain.

Stilwell (1957) examined the deep fascia of embalmed human cadavers and the nerve supply of the plantar, crural, thigh regions of the lower extremity, palmar and dorsal aspect of the hand and the wrist, the antebrachial regions of the upper extremity, and the deep dorsal thoracic and lumbar fasciae. The same regions were stained intravitally with methylene blue solutions in *Macaca mulatta* and rabbits. The author emphasized the presence of numerous free nerve endings and simple, small, encapsulated endings in the fasciae and examined several differences between the regions. However, it should be noted that a nerve type analysis was not performed on these human specimens and that the method of identification of the termination of small nerves is not mentioned. Stecco et al. (2007) studied the innervation of the deep fascia of the upper limb as part of an anatomical study. The specimens were taken from the expansion of the pectoralis major onto the bicipital fascia, the middle third of the brachial fascia, the lacertus fibrosus, the middle third of the antebrachial fascia, and the flexor retinaculum. The authors found the presence of nerve elements in all the specimens with differences between the areas. The observed receptors included Pacini and Ruffini corpuscles mechano-receptors and numerous free nerve endings surrounding the vessels, regularly distributed amongst the fibrous components. A large number of receptors were found in the retinacula compared to other areas. The type of free nerve endings observed was not characterized or examined. The authors highlight the point that the intra-fascial free nerve endings were frequently perpendicularly oriented to the collagen fibers, thereby, increasing the likelihood of their activation by the stretching of the collagen fibers. Stecco et al. (2018a,b) investigated the innervation of the palmar aponeurosis by comparing the pathological palmar aponeurosis vs. the non-pathological palmar aponeurosis. Pathological samples were obtained from Dupuytren's disease patients; the other samples were taken from unembalmed cadavers. Specimens from the flexor retinaculum were utilized for control and comparison. The authors emphasized that these two elements, the flexor retinaculum, and palmar aponeurosis, can be considered as specialized components of the deep fascia of the upper limbs. Anti-S100 protein and anti-tubulin antibodies were used to immunohistochemically stain all the samples. The authors clarified the density and location of the nervous structures indicating that: (1) the palmar aponeurosis showed a higher density of free nerve endings than the retinacula, Pacini corpuscles, and Golgi-Mazzoni corpuscles; (2) the pathological samples showed a higher density of free nerve endings than the non-pathological samples. The authors concluded that the nervous structures are involved in the augmented fibrosis of Dupuytren's disease and emphasized the importance of fascial innervation in the nociception. A similar observation regarding the innervation of pathological tissues was previously reported by Sanchis-Alfonso and Rosello-Sastre (2000) who studied the patellar lateral retinacula. The specimens were excised during Insall proximal realignment surgeries or isolated lateral retinacular release surgeries, performed on patients suffering from an isolated symptomatic patellofemoral malalignment. The specimens were evaluated for the neural markers, neurofilament protein, S-100 protein, substance P, and the nerve growth factor (NGF). The data from the study exhibited growth of the myelinated and unmyelinated nerves with a prime nociceptive component into the lateral retinaculum,

mostly surrounding the blood vessels. According to the authors, this nerve ingrowth is a result of repeated injury and due to improper healing process and may also be a major component in the chronic pain characteristic of the above pathology.

Fascia and soft tissue innervation in the human hip and their possible role in post-surgery pain have recently been investigated (Fede et al., 2020). Samples were collected during hip hemiarthroplasty surgery performed after a traumatic femoral neck fracture. The different layers of the specimens, i.e., skin, superficial adipose tissue, superficial fascia, deep adipose tissue, deep fascia, muscles, capsule, capsule ligament, ligamentum teres, and tendons were evaluated and quantified by the anti-S100 antibody for myelin-forming Schwann cells. Staining was employed to obtain the percentage of antibody positivity, density, and mean diameter of the nerve fibers. After skin and superficial fascia (64.0 ± 5.2, 33.0 ± 2.5 number/cm^2, respectively), the deep fasciae and ligaments (19.0 ± 5.0 & 22.0 ± 5.1, number/cm^2, respectively) were found to be the most highly innervated tissues invaded by networks of small nerve fibers, specifying, a possible role in post-operative pain. On the other hand, the hip joint capsule and the tendon (12.0 ± 6.1, 11.0 ± 0.8 number/cm^2, respectively), showed the lowest density of nerves. These findings, according to the authors, indicate that the capsular injury plays a minor role in post-operative pain compared with other tissues examined in the study.

3.2. Experimental in vivo studies

For the last 10 years, studies have been exploring the probability that deep fascia is a source of various pain syndromes. The aim of these studies was to provoke nociceptive responses under in-vivo conditions by using mechanical, chemical, and electrical stimuli (solely or combined),. In an experiment conducted by Pedersen et al. (1956), the thoracolumbar fascia of decerebrated cats was mechanically pinched by forceps, producing contractions of the back, gluteal, and hamstring muscles on the same side. Pinching the muscles under that area produced a significantly reduced response than thoracolumbar fascia pinching. Using the same concept of mechanical stimulation, Taguchi et al. (2008, 2013) pinched the thoracolumbar fascia and the crural fascia of rats. In the first experiment (Taguchi et al., 2008), the authors focused on the posterior layer of the thoracolumbar fascia. The pinching procedure produced a response in a significant number of neurons in the spinal cord dorsal horn. A similar response was obtained by irritating the posterior layer of the thoracolumbar fascia with hypertonic saline, considered an effective way to stimuli type VI afferents. These findings represent, in the authors' opinion, the nociceptive capacity of the thoracolumbar fascia. In the second experiment, Taguchi et al. (2013) pinched the rat crural fascia and found in the spinal dorsal horn, at levels L2 to L4, an increased expression of c-FOS, a marker of neural activation induced by tissue injury and nociceptive stimulation. The c-FOS expression was higher by ~2.5 times when compared to cutting the skin which served as a sham stimulus procedure.

The concept of a hypertonic saline injection as a pain generator was implemented by Gibson et al. (2009) in a study examining the nociceptive responses to fascial stimulation. The study was conducted on rats when, before injection, delayed onset muscle soreness (DOMS) was inducted in one of the lower limbs. Their research data revealed that an injection of hypertonic saline into the deep fascia of the leg with the DOMS, provoked substantial pain responses, compared with the pain responses when the hypertonic saline was injected into the muscle itself or the muscle of the contralateral leg. The authors point out that since micro-injuries and inflammation are suspected as a major cause of pain in DOMS, it may also indicate the high feasibility of a fascial nociceptive contribution to the DOMS phenomenon. Schilder et al. (2014) used the same concept of hypertonic saline injection in a human trial where hypertonic saline was injected into the thoracolumbar fascia and the muscular tissues beneath. The results demonstrated that hypertonic saline stimulation of the thoracolumbar fascia tends to induce pain for a longer duration (~15 min) than an injection into related muscular tissues (~10 min). The intensity of pain was similarly reported by the participants. The authors pointed out that an injection into the fascia, but not into the muscular tissue, triggered verbal pain descriptions, such as agonizing, heavy, and killing. This type of terminology is often used by patients with low back pain to describe their pain sensations.

Deising et al.'s study (2012) of human volunteers found that by injecting NGF into the thoracolumbar fascia at the lumbar level of L4-L5, prolonged sensitization to mechanical pressure occurred during the first day and up to one week. A similar reaction was observed when chemical stimulation by an acidic solution was applied to the irritated area, up to two weeks post-stimulation. The authors note that NGF has been proposed as one of the possible causes of exercise-induced muscle soreness, suggesting that the muscle fascia nociceptors influence muscular pain syndromes, mediated by NGF-induced sensitization processes.

Weinkauf et al. (2015) utilized this same procedure in a group of human volunteers when the NGF was injected into the target tissues, the tibialis anterior muscle, and the contralateral fascia of the tibialis anterior muscle. In a second group, the NGF was injected into the muscles of one side and the contralateral thoracolumbar fascia at the L4 lumbar level. The results of the study indicate that the spatial extent of mechanical hyperalgesia (i.e., sensitivity in a distant area from the injection site) to blunt pressure and injections of low pH solutions, significantly differ between lumbar and tibial sites and between fascia and muscle. Mechanical hyperalgesia, at the lumbar sites, was recorded as 19 ± 6.6 mm when injected in the fascia and 9 ± 6 mm in the muscles. In the tibial injection sites, an extension of sensitization was significantly larger than in the lumbar sites and significantly larger in the fascial injection site (49 ± 17 mm) compared with the muscle injection site (23 ± 13 mm), indicating a high probability of the paraspinal fascia as a major contributor to low back pain.

Hoheisel and Mense (2015) injected a complete Freund's adjuvant, a solution of antigen emulsified in mineral oil with inactivated and dried mycobacteria in order to inflame the thoracolumbar fascia of rats. Animal dorsal horn neurons at the level of spinal segment L3 were recorded 12 days after the injection, revealing that the proportion of neurons with input from all deep somatic tissues rose from 10.8% to 33.3% in the experimental group compared to the controls (injected with isotonic saline). In addition, the authors mentioned several interesting findings: (1) neurons in the spinal segment L3 usually have no input from the fascia, however, inflamed fascia activated 11.1% of the L3 neurons; (2) an appearance of new receptive fields from the deep tissues of the hind limb was observed; (3) identical behavioral changes in the animals of the experimental group were manifested as a less exploratory activity, which normally characterizes them, and was not observed in the controls. According to the authors, the above findings can explain some of the symptoms of pain distribution associated with nonspecific low back pain as manifested in humans.

Electrical stimulation was used by Lau et al. (2015) to investigate changes in the electrical pain threshold after repeated eccentric exercise. The trial was conducted on humans performing two eccentric exercise bouts. The electrical pain threshold was assessed in the biceps brachii fascia, biceps brachii muscle, and brachialis fascia, one day before, immediately after, and on the first, second, and fourth days after exercise. Pain threshold was measured

separately by a pulse algometer (UPA-301, Unique Medical Co Ltd, Tokyo, Japan); the correct location of the needle was confirmed using a real-time B-mode ultrasound system. The results of the recordings showed that the fascia is more sensitive to electrical stimulation than the muscle after eccentric exercise and that inflamed or damaged fascia contributes and is associated with DOMS more than muscle fibers. These findings are consistent with Gibson et al.'s (2009) study conducted on 16 healthy human volunteers. Schilder et al. (2016) employed electrical stimulation (high-frequency pulses; 5 × 100 pulses at 100 Hz; HFS) to stimulate the multifidus muscle and the overlying thoracolumbar fascia at lumbar levels L3-L4, using two bipolar concentric needle electrodes and an ultrasound device for correct positioning. Perceived pain was measured by a numerical rating scale. The trial results demonstrated that the electrical stimulus when applied to the thoracolumbar fascia, induces intense pain and produces long-term potentiation, which was not obtained when the stimulus was applied to the muscle. Long-term potentiation is assumed to be linked to pain amplification and potentially to chronic pain development. Accordingly, the authors suggested that the thoracolumbar fascia may play an important role in nonspecific low back pain.

In a later study, using the same principle of electrical stimulation, Schilder et al. (2018) concentrated on the evaluation of pain quality described verbally, and the differences between a nociceptive pain description in a thoracolumbar fascia stimulation and muscle stimulation in humans. The results demonstrated distinct pain quality patterns between the muscle, fascia, and skin. Whereas "heat pain" or "sharp pain" were more associated with the fascia and skin, the "deep pain" description was linked to an irritation of the muscles. These results were published again (Schilder 2019) with an emphasis on the difference in the verbal description of pain produced by stimulation of fascial, skin, and muscle, indicating that fascial stimulation with high-frequency electrical stimulation, generated intense pain and induced long term potentiation effects, in contrast with the short-lasting potentiation effects when the same stimulation was applied to the underling multifidus muscle.

4. Conclusions

Reviewed data indicate that different components of the deep fascia, both in humans and animals, are richly innervated. These fascial components usually exhibit dense innervation, comprising amongst others, nociceptive afferents and therefore, can also be considered as pain-sensitive structures (Wilke et al., 2017; Hoheisel et al., 2015; Mense and Hoheisel 2016; Corey et al., 2011; Tesarz et al., 2011; Barry et al., 2015; Simons et al., 2018). Moreover, the reviewed studies indicate that the application of different types of stimuli, electrical, mechanical, and chemical to these fascial components, produces long-lasting, sometimes severe pain responses. The intensity and severity of pain produced by the stimulation of fascia were, in some cases, higher than ones produced by the stimulation of the related muscular tissue.

A mechanism of fascia intermediated pain comprises microinjuries that irritate nociceptive nerve endings in the fascial tissue, thus, inducing local pain and occasionally, referred pain to a remote area (Weinkauf et al., 2015). In addition, it appears that structural changes due to chronic overloading/overuse - i.e., in the patellar retinacula (Sanchis-Alfonso and Rosello-Sastre 2000), Dupuytren's disease (Stecco et al., 2018), or microinjury, i.e., delayed onset muscle soreness (Gibson et al., 2009; Lau et al., 2015), compromise proprioceptive signaling and an increase in nerve quantity and receptive field. These observations are compatible with similar connective tissue diseases (i.e., Achilles tendinosis, patellar tendinopathy, and thoracolumbar inflammation) wherein the new growth of substance P-positive nerve fibers is observed, indicating involvement in nociception, as well as fibroblast stimulation (Stecco et al., 2018). Another interesting point, not reviewed in the present paper, but presented in the reviewed studies, (Wilke et al., 2017; Hoheisel et al., 2015; Stecco et al. 2007, 2018; Sanchis-Alfonso and Rosello-Sastre 2000; Fede et al., 2020), is the role of the fascia in the proprioceptive system, with the presence of mechanoreceptor nerves ending in the various components of the fascia. These findings, combined with mechanical or functional changes of the fascia observed in different pathologies or pain syndromes, can indicate the potential role of fascia as a possible source of musculoskeletal morbidity. This connection between fascial function and morbidity is beyond the scope of the present review and should be further investigated.

The observations presented in this review could indicate that the deep fascia, and its various components (i.e., thoracolumbar fascia, ankle retinacula, aponeurotic fascia, etc.), might be a source of musculoskeletal pain as a primary pain generator or can play a certain role in various pain syndromes (i.e., discogenic pain, nonspecific low back pain, various tendinopathies or ligaments-originated pain, etc.).

5. Clinical relevance

- The deep fascia is a plausible source of nociception and should always be taken into consideration during a patient evaluation.
- Manual and physical therapies applied and aimed at the deep fascial tissue can be of significant value in the treatment of different pathologies and various pain syndromes.

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Declaration of competing interest

None.

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