Introduction

This paper discusses the definition of a common, but incompletely understood syndrome associated with soft tissue pain, referred to as myofascial pain syndrome (MPS). It begins with a description of the syndrome and its frequently associated finding, the myofascial trigger point (MTrP). The paper describes current published data about biochemical, mechanical, and physical properties of the MTrPs and the surrounding tissue.

There are no proven models explaining the cause of MPS or MTrPs, and the pathophysiology of both is conjectural at this point. Therefore, the majority of the discussion will center around descriptions of the syndrome, hypotheses, and data supporting the etiology based on existing literature and approaches toward treatment of MTrPs and symptom control of myofascial pain.

Description of Myofascial Pain Syndrome and Myofascial Trigger Points

Myofascial pain syndrome (MPS) is a descriptive term used to define an acute or chronic soft tissue musculoskeletal pain condition. It is characterized by sensory, motor, and autonomic findings associated with myofascial trigger points (MTrPs).1,2 The findings may be local to MTrPs or may be distant, with a referred pain pattern. It often involves the neck and back1 and has a high prevalence in primary care settings. MPS was diagnosed in 21% of the patients seen in a general orthopedic clinic and 30% of the patients seen at an internal medicine group practice.3 Myofascial pain is poorly understood and frequently not diagnosed.4 It is the leading cause of job-related disability and the second leading cause of disability in the US, costing Americans more than $50 billion each year.5

Chronic soft tissue pain, of which MPS may be an example, is a pathologic state with a spectrum of clinical signs and symptoms. The experience of pain is a multidimensional process that may include sensory components and perceptions that may result in aversive behaviors, all of which involve activation of different areas of the central and peripheral nervous system. Its origin may be secondary to tissue damage in which there is a lowering of pH and release of histamines and bradykinin locally. C fibre response may be up-regulated peripherally by serotonin, prostaglandins, thromboxane, and leukotrienes as a result of tissue hy-
poxia and trauma. Substance P may also be released peripherally with resultant increase in peripheral vasodilation and further sensitization of the C fibre’s peripheral ending. This may stimulate small, non-myelinated C fibres, generating an electrical impulse which travels to the dorsal horn of the spinal cord. Even chemical products of tissue breakdown may sometimes enter the neuron and be transported centrally to exert an effect at the dorsal horn synapse areas of the central and peripheral nervous system. The condition resulting from the upregulation is peripheral sensitization. By comparison, the International Association for the Study of Pain has defined central sensitization as: “Increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub-threshold afferent input” and is thought to occur at the dorsal horn. Both central and peripheral sensitization are likely to occur in chronic pain patients. These types of sensitization involve nociception, a phenomenon which results from an actual or potential tissue damaging event transduced and encoded by nociceptors. Nociceptors are sensory receptors that are capable of transducing and encoding noxious stimuli. Persistent symptoms may be the result of peripheral sensitization of nociception. In addition, central sensitization, modulation, and structural modification also play an important role. Signs of peripheral and central sensitization are allodynia (pain due to a stimulus that does not normally provoke pain) and hyperalgesia (an increased response to a stimulus that is normally not painful).

MTrPs are hard, palpable, discrete, localized nodules located within taut bands of skeletal muscle, which are painful on compression. MTrPs can be either active (A-MTrP) or latent (L-MTrP). An A-MTrP is associated with spontaneous pain (pain is present without palpation). This spontaneous pain can be at the site of the MTrP or remote from it. However, firm palpation of the A-MTrP increases pain locally and usually reproduces the subject’s remote pain. A L-MTrP is not associated with spontaneous pain, although pain can often be elicited in an asymptomatic subject by a mechanical stimulus such as finger pressure over it. A visible local twitch response (LTR) can be elicited during mechanical stimulation of the MTrP. The LTR is a transient, rapid contraction of a taut band of muscle fibers and is characteristic of MTrPs. A significant number of asymptomatic adults (such as 45% of healthy American Air Force personnel) have L-MTrPs. In someone with a spontaneous pain complaint, thorough palpation of the myofascial tissue is required to identify and differentiate a A-MTrP from a L-MTrP. Pain elicited by palpation of a L-MTrP in a symptomatic subject is qualitatively different from the subject’s pain complaint.

MTrPs are highly prevalent in selected populations: 85–93% of patients with chronic pain disorders presenting to specialty pain management centers have MPS. A-MTrPs were the primary source of pain in 74% of 96 patients with musculoskeletal pain seen by a neurologist in a community pain medical center and in 85% of 283 patients consecutively admitted to a comprehensive pain center. MTrPs have been associated with tension-
type headaches,\textsuperscript{14} neck and low back pain,\textsuperscript{12} and pelvic pain.\textsuperscript{1} A study of 110 adults with migraine headaches showed that 94\% of the patients reported migrainous pain with manual stimulation of cervical or temporal MTrPs compared to 29\% of controls.\textsuperscript{14} MTrPs have been associated with numerous other pain conditions including radiculopathies, joint dysfunction, disc pathology, tendinitis, craniofacial dysfunction, migraines, carpal tunnel syndrome, whiplash-associated disorders, spinal dysfunction, post-herpetic neuralgia, and complex regional pain syndrome.\textsuperscript{1,15}

The Unique Neurobiology of Muscle Pain

Muscle pain has a very unique neurobiology which helps explain its clinical presentation. In contrast to cutaneous pain, muscle pain causes an aching, cramping pain that is difficult to localize and is often referred to deep and distant somatic tissues. Muscle pain activates unique cortical structures in the central nervous system, particularly those which are associated with the affective or emotional components of pain. Muscle pain is inhibited more strongly by descending pain-modulating pathways, and activation of muscle nociceptors is much more effective at inducing maladaptive neuroplastic changes in dorsal horn neurons.\textsuperscript{16} These neuroplastic changes are important harbingers of a chronic pain syndrome.

Central sensitization is a hallmark in the transition from normal to aberrant pain perception—i.e., when the central nervous system (CNS) experience of pain outlasts the noxious stimulus coming from the periphery. Peripheral sensitization of group IV afferents in the muscle is especially effective at driving central sensitization. In animal models of pain, nociceptive input from skeletal muscle is much more effective at inducing neuroplastic changes in the spinal cord than noxious input from the skin.\textsuperscript{17}

Continuous activation of muscle nociceptors increases the “afferent drive,” that is, the impulses per second bombarding dorsal horn neurons in the spinal cord. This may lead to changes in function and connectivity of sensory dorsal horn neurons via central sensitization.\textsuperscript{18} This process can spread to adjacent neurons, leading to structural changes and maladaptive neuroplastic alterations in the central nervous system. For example, there may be loss of inhibitory neurons at segmental levels affected by the persistent noxious input.\textsuperscript{19} The clinical consequences are
allodynia (pain in response to a normally non-painful stimulus), hyperalgesia (increased sensitivity to pain), and expansion of the receptive field of pain. These clinical signs of central sensitization, which result in an intensified pain experience, are very distressing to patients.

There is a biochemical basis to the development of peripheral and central sensitization in muscle pain. For example, sensitizing agents released in muscle may up-regulate or increase the activity of receptor molecules on the nociceptor terminal. Continuous activation of muscle nociceptors leads to the co-release of substance P and glutamate at the pre-synaptic terminals of the dorsal horn. This can eventually lead to maximal opening of calcium-permeable ion channels, which hyperexcites nociceptive neurons and induces apoptosis of inhibitory neurons. Moreover, prolonged noxious input may lead to long-term changes in gene expression, somatosensory processing, and synaptic connections in the spinal cord and other higher structures. In addition, previously silent synapses may become effective. These mechanisms of peripheral and central sensitization lower the activation threshold of afferent nerves and their central terminals, allowing them to fire even in response to daily innocuous stimuli. Consequently, even non-noxious stimuli such as light pressure and muscle movement can cause pain.

**Biochemical and Tissue Properties of MTrPs**

Although the specific pathophysiological basis of MTrP development and symptomatology is unknown, several promising lines of scientific study (i.e. histological, neurophysiological, biochemical, and somatosensory) have revealed objective abnormalities. It has been observed that MTrPs tend to occur most frequently in Type 1 muscle fibers. Slow motor units are always stiffer than fast units, although fast units can produce more force. Traumatic muscle fiber injury during sustained sub-maximal level exertions could lead to the development of an MTrP. Acute muscle overload can occur with direct impact and lifting injuries. The Cinderella Hypothesis postulates that during low-level static continuous muscle contractions, smaller (type 1) muscle fibers are the first to be recruited and the last to be de-recruited and use only a fraction of motor units available (Henneman’s “size principle”). As a result, these “Cinderella” fibers are continuously activated and metabolically overloaded. Accordingly, sub-maximal muscle exertions (e.g., contraction of trapezius muscle during postural maintenance), may cause possible damage to the sarcomere assembly and disturbance of Ca²⁺ homeostasis—features believed to be precursors to the formation of MTrPs and the onset of MPS.
Typical motor abnormalities seen in people with A- and L-MTrPs may be associated with motor weakness and stiffness as a result of restricted range of motion. The contribution of the MTrP to this tissue stiffness is currently a very active area for investigations. In the last decade, a new modality for tissue characterization termed Elasticity Imaging (EI) or elastography has emerged. EI is based on generating a stress in the tissue using various static or dynamic means and measuring resulting strain by ultrasound or MRI. There are an increasing number of publications on elastography that have been applied to most organ systems. Magnetic resonance elastography (MRE), which uses a modified gradient echo pulse sequence to image the propagation of induced vibration shear waves, can be used to measure the viscoelastic properties of skeletal muscle. Recently, one study utilized MRE to show that the shear wave propagation pattern in the taut band in the upper trapezius was different compared to palpably normal muscle. This study did not specifically identify MTrPs within the taut band but did not exclude this as a possibility. Our group has shown that ultrasound elastography can be used for imaging MTrPs and that muscle surrounding MTrPs appears stiffer on ultrasound scanning.

MTrPs in histological studies in animals are localized contractions of sarcomeres into knots or nodules with disruption of normal fiber structures. Similar morphology can be induced by locally blocking AChE. These resulting lesions have been hypothesized to be similar to MTrPs. One study shows evidence of muscle spindles, while the other shows contraction knots and abnormal muscle fiber contracture. However, biopsy evidence from human studies is very limited.

A key aspect of the Integrated Hypothesis is that muscle fiber contracture at MTrPs can cause capillary constriction, decreasing perfusion and leading to tissue hypoxia. A study of tissue oxygenation in MTrPs using a customized oxygen sensor indicated a focal region of hypoxia at the center of the palpable nodule and a surrounding region of hyperoxia. Histological evidence suggests that MTrPs are sites of tissue distress. Inflammation, hemodynamic stress, and hypoxia, and tissue distress may lead to vascular remodeling in the neighborhood of MTrPs. One investigation has demonstrated that circulatory disturbances secondary to increased intramuscular pressure may also lead to the development of myalgia. The Integrated Hypothesis does not suggest that trauma may be a plausible explanation for the pathophysiology. Nonetheless, small muscle tears, due to persistent contraction has not been ruled out as a contributor to the pathophysiology.

The biochemical conditions associated with this hypothesis asserts that the primary dysfunction is an abnormal increase in the production and release of

Figure 5. (A) Subject with an active MTrP visible as a hypoechoic region on the grayscale image (arrow), and an artery running through the MTrP visible on color Doppler. (B) High-resistance blood flow waveform with reverse diastolic flow in the artery through the a-MTrP. (C) The same subject had a latent MTrP on the contralateral side with an artery running through it, which showed no reverse diastolic flow. (Sikdar, 2009)
The observed waveforms of arteries in the neighborhood of MTrPs showed high-resistance blood flow with retrograde diastolic flow in the region of the A-MTrPs. This differed from the blood flow from the surrounding tissue of the L-MTrPs and normal uninvolved myofascial tissue. We believe that an increase in vascular resistance in A-MTrPs is consistent with blood vessel compression due to sustained contracture at or near the trigger point, or there may be vessel constriction due to oxidative stress or hypoxia. The blood vessel compression may be sufficient or one of a number of contributing factors that lead to local hypoperfusion or hypoxia. Ischemic tissue is often associated with pain, tenderness, and nodularity of an A-MTrP. The retrograde diastolic flow suggests a substantial vascular volume upstream of the constriction, where the blood accumulates in systole and is emptied retrograde in diastole since the antegrade path is obstructed. This is consistent with vascular remodeling in the neighborhood of active MTrPs.

The transformation of a tender nodule into a myofascial pain syndrome is poorly understood. However, local muscle pain is known to be associated...
with the activation of muscle nociceptors by a variety of endogenous substances including neuropeptides, arachidonic acid derivatives, and inflammatory mediators, among others.\textsuperscript{38} Recent biochemical studies by our investigative group (39, 27) using a microdialysis technique confirmed that patients with A-MTrPs in the upper trapezius have significantly elevated levels of protons, bradykinin, pro-inflammatory cytokines (tumor necrosis factor (TNF)-\(\alpha\), interleukin(IL) 1-\(\beta\), interleukin(IL)-6, interleukin(IL)-8), neuropeptides (CGRP, substance P), and catecholamines (serotonin, and nor-epinephrine) within the local milieu of the A-MTrP compared to those with a L-MTrP or normal tissue.

We did not assay for possible contributors of the arachadonic pathway in prior work nor did we assay for cellular changes. The reduced oxygen levels in A-MTrP, and increased metabolic demand results in a local energy shortage and a local shortage of ATP.\textsuperscript{39} Under normal physiologic circumstances, ATP at pre-synaptic membranes of the motor neuron inhibits the release of acetycholine (ACh). Decrease in ATP leads to increased ACh release and prolonged muscle contraction. Moreover, insufficient ATP at the motor end-plate results in a failure of the calcium pump, increased levels of sarcoplasmic Ca\(^{2+}\), and a Ca\(^{2+}\)-induced Ca\(^{2+}\) release from the sarcoplasmic reticulum, which further reinforces sarcomere contractures.

Calcitonin gene-related peptide can enhance the release of ACh from the motor endplate and simultaneously decrease the effectiveness of acetylcholinesterase (AChE) in the synaptic cleft, which decreases the removal of ACh.\textsuperscript{40,41} Calcitonin gene-related peptide also upregulates the ACh-receptors (AChR) at the muscle and thereby creates more docking stations for ACh. Miniature endplate activity depends on the state of the AChR and on the local concentration of ACh, which is the result of ACh-release, reuptake, and breakdown by AChE. In summary, increased concentrations of CGRP lead to a release of more ACh, and increase the impact of ACh by reducing AChE effectiveness and increasing AChR efficiency. Miniature endplate potential frequency is increased as a result of greater ACh effect.

The observed lowered pH has several implications as well. Not only does a lower pH enhance the release of CGRP, it also contributes to a further down-regulation of AChE. The multiple chemicals and lowered pH found in active MTrPs can contribute to the chronic nature of MTrPs, enhance the segmental spread of nociceptive input into the dorsal horn of the spinal cord.

### Treatment

Current approaches for pain relief of MPS include pharmacological and non-pharmacological interventions. Anti-inflammatory, analgesic, and narcotic medications have been used for symptomatic control. Non-pharmacological interventions have been used for decades among a broad based group of investigators.\textsuperscript{1,2} Specifically, these have included manual therapies, massage, spray and stretch techniques, among others.\textsuperscript{42,43} A recent publication has shown the effectiveness of manual therapies in a controlled, blinded, single-assessor controlled trial.\textsuperscript{44}

A frequent practice, which has approached acceptance as “standard of practice”, is the use of soft tissue needling. This technique involves the use of a small, 30 gauge needle, and the infiltration of a small amount of anesthetic and/or steroid, or the use of needling without injection and massage therapy. The lack of objective clinical outcome measures has been a barrier for critically evaluating the efficacy of these therapeutic methods. All of these factors have led to a lack of consensus on myofascial pain as a clinical entity and have contributed to the uncertainty about the pathogenesis and pathophysiology of trigger points. Therefore, there is a need to develop objective, repeatable, and reliable diagnostic tests for evaluation and treatment outcome measures for MTrPs. Such measures can be used to properly diagnose and understand the natural history of MTrPs and to determine the underlying mechanisms and relevance to the development and resolution of myofascial pain.

Gerwin and Dommerholt have written extensively on the evaluation of several treatment options includ-
ing trigger point injections and dry needling. Local anesthetics (e.g. procaine, lidocaine, bupivacaine), isotonic saline, nonsteroidal anti-inflammatories, bee venom, and botulinum toxin have all been studied as potential injectables. Studies have found that 0.25% lidocaine is an effective therapy while nonsteroidal anti-inflammatory medication, steroids, and vitamin B<sub>12</sub> are not as effective. Although serotonin antagonists are not available in some locations throughout the world, tropisetron, a serotonin antagonist, has been found to be more effective than lidocaine in two German studies.\textsuperscript{46,47}

Advancing a needle into a trigger point that does not have a lumen is a technique called dry needling. Evidence was first introduced\textsuperscript{48} about the use of dry needling techniques as a clinical approach by Lewit in 1979.\textsuperscript{49} It was demonstrated to produce analgesia in 87% of subjects, many of whom had lasting effects. The mechanism by which this was thought to work was a mechanical stimulation. Clinicians using this technique have attempted to produce a twitch response, which is an involuntary spinal cord reflex of the muscle fibers in the taut band. This twitch can be seen, palpated, and recorded on an oscilloscope if performed using electromyography. Our group has demonstrated that there is a rapid change in the biochemical milieu following the twitch and that this change restores the surrounding biochemical (cytokines, neuropeptides, and catecholamines) to a profile that is consistent with that of I-MTRPs and normal tissue.\textsuperscript{27} In particular, there is a significant drop in substance P and calcitonin gene-related peptide, providing evidence supporting the role of these two substances in MPS.\textsuperscript{27}

The additional information about biochemicals in the surrounding milieu of the MTrP does not provide adequate information to establish a mechanism by which dry needling works to relieve pain. The proposed mechanism involving stimulation of A<sub>D</sub> sensory afferent fibers are has not been supported by all biochemical research findings.\textsuperscript{39} Hormones, neuropeptides, and cytokines other than those reported by our team\textsuperscript{39} may play an important role in pain initiation and persistence, such as opioids and oxytocin, but these have not been conclusively demonstrated.

Despite the absence of a proven mechanism by which dry needling works, and despite the lack of a mechanism explaining the development of TrPs, clinical practice and some clinical trial evidence\textsuperscript{44,48} have generated evidence for the use of this approach in an ever expanding group of practitioners.

Summary

The published data on the prevalence and clinical presentation and impact on function of MPS and MTrPs indicate that this syndrome is of concern to patients and practitioners. However, there also a common physical finding in asymptomatic individuals. This dichotomy challenges and behooves pain management practitioners to learn how to distinguish active from latent MTrPs. Making this distinction is critical in order to accurately identify and treat a myofascial component of pain.

Fortunately, advances in the field have enabled us to better describe and physically characterize the trigger point and its surrounding milieu using imaging, in particular ultrasound, and microanalytic approaches. These are likely to serve as objective, reliable, and sensitive measures for diagnosis and for measuring treatment efficacy. Future research will be needed to identify the pathophysiology and etiology of the syndrome, enabling us to target treatments toward prevention, early intervention, and effective treatments.

REFERENCES


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**Naomi Lynn Gerber, M.D.**

Dr. Gerber, Professor of Global and Community Health and Director of the Center for Study of Chronic Illness and Disability, is responsible for developing a research program to help describe the mechanisms by which disease produces disability and explore treatments that can prevent or reduce disabilities and restore function. Dr. Gerber served as Chief of the Rehabilitation Medicine Department (RMD) in the Clinical Center of National Institutes of Health (NIH), a position held from 1975–2005. In this capacity, she assured the quality of Physical Medicine & Rehabilitation (PM&R) service for all referred NIH patients with impairments & disability. She is board certified in internal medicine, rheumatology, and PM&R. Much of her clinical research interest has been centered on measuring and treating impairments and disability in patients with musculoskeletal deficits; in particular, children with osteogenesis imperfecta, and persons with rheumatoid arthritis and cancer. Dr. Gerber now serves on the Board of Governors of the Academy of Physical Medicine and Rehabilitation. Dr. Gerber has authored/co-authored 90 peer reviewed, published manuscripts and 45 Chapters in major textbooks (Internal Medicine, Rheumatology, Cancer, Rehabilitation et al.)