Muscle Pain: Diagnosis and Treatment

Bearbeitet von
Siegfried Mense, Robert D Gerwin

1. Auflage 2010. Buch. xiv, 366 S. Hardcover
ISBN 978 3 642 05467 9
Format (B x L): 15,5 x 23,5 cm
Gewicht: 800 g

Chapter 2
Myofascial Pain Syndrome

Robert D. Gerwin

Contents

2.1 Introduction 17
2.1.1 Trigger Point Manifestations 18
2.1.2 Trigger Point Pain 18
2.1.3 Current State of Knowledge 19
2.2 Clinical Presentation 20
2.3 Definition 20
2.3.1 Primary Trigger Point Characteristics 20
2.3.2 Additional Trigger Point Characteristics 21
2.3.3 Trigger Point Identification 23
2.3.4 Weakness 24
2.3.5 Recruitment 24
2.3.6 Reciprocal Inhibition 24
2.3.7 Range of Motion 25
2.3.8 Functional Adaptation 25
2.4 Sensory Changes 25
2.5 Electrophysiology of the Trigger Point: Spontaneous Electrical Activity (Endplate Noise) 26
2.6 Etiology of Myofascial Trigger Points 28
2.6.1 Generation of the Taut Band 28
2.6.2 Muscle Overuse Syndromes and Myofascial Pain Syndrome 28
2.6.3 The Neuromuscular Junction: The Role of the Neuromuscular Junction in Trigger Point Formation 28
2.6.4 Peripheral Nerve Sensitization in Myofascial Pain Syndrome 30
2.6.5 Hypoxia and Ischemia 30
2.6.6 Biochemistry of the Trigger Point Region 31
2.7 Muscle Pathology 33

R.D. Gerwin (✉)
Associate Professor of Neurology, Johns Hopkins University, Baltimore, Maryland 21287, USA; Pain and Rehabilitation Medicine, 7830 Old Georgetown Road, Suite C-15, Bethesda, MD 20814-2432, USA
e-mail: gerwin@painpoints.com

S. Mense and R.D. Gerwin (eds.), *Muscle Pain: Diagnosis and Treatment*,
DOI 10.1007/978-3-642-05468-6_2, © Springer-Verlag Berlin Heidelberg 2010

2.8 Central Sensitization 37
2.8.1 Central Pathways 37
2.8.2 Referred Pain 38
2.9 Muscle Stress and Overuse 40
2.9.1 Muscle Overuse Syndromes 40
2.9.2 Postural Stresses 43
2.10 Pain Initiation in Myofascial Pain Syndrome 43
2.10.1 Inflammatory Pain Models 43
2.10.2 Acid-Sensing Ion Channels 44
2.10.3 Serotonergic Mechanisms 44
2.10.4 Calcitonin Gene-Related Peptide 45
2.10.5 Spinal Modulation of Pain 45
2.11 Epidemiology of Myofascial Pain 46
2.11.1 Prevalence Studies 46
2.11.2 Gender Differences 46
2.11.3 Hypermobility 47
2.12 Diagnosis of Myofascial Pain Syndrome 47
2.12.1 Reliability of Manual Identification of Trigger Points 47
2.12.2 Consensus Studies and Systematic Reviews 49
2.12.3 Objective Criteria 50
2.12.4 Pain from Bone and Tendon 51
2.13 Differential Diagnosis 52
2.13.1 Differential Diagnostic Considerations 52
2.13.2 Trigger Point-Initiating Factors 52
2.13.3 Fibromyalgia 53
2.13.4 Other Disorders to Consider 53
2.13.5 Viscerosomatic Disorders 53
2.13.6 Other Causes of Referred Pain 54
2.13.7 Mechanical Dysfunction 54
2.14 Treatment 54
2.14.1 Treatment Principles 54
2.14.2 Manual Inactivation of Trigger Points 55
2.14.3 Noninvasive, Non-Manual Treatment Techniques 57
2.14.4 Invasive Treatment of Myofascial Trigger Points 57
2.14.5 Botulinum Toxin 60
2.15 Perpetuating Factors 61
2.15.1 Introduction to Perpetuating Factors 61
2.15.2 Iron Insufficiency 61
2.15.3 Hypothyroidism 62
2.15.4 Iron Status and Thyroid Function 63
2.15.5 Vitamin D Deficiency 64
2.15.6 Statins 65
2.15.7 Structural and Mechanical Factors 66
2.16 Selected Specific Clinical Syndromes 66
2.16.1 Headache 66
2.16.2 Fibromyalgia 67
2.16.3 Endometriosis and Other Pelvic Viscerosomatic Pain Syndromes 68
2.16.4 Radiculopathy 69
2.16.5 Thoracic Outlet Syndrome 70
2.17 Conclusion 71
References 71

Abstract Myofascial pain syndrome (MPS) is a form of myalgia that is characterized by local regions of muscle hardness that are tender and that cause pain to be felt at a distance, i.e., referred pain. The central component of the syndrome is the trigger point that is composed of a tender, taut band. Stimulation of the band, either mechanically or with activity, can produce pain. The active trigger point has identifiable pathophysiologic changes. The concentrations of a number of substances are measurably elevated in the milieu of the active trigger point, namely substance P, CGRP, bradykinin, and assorted cytokines, indicating that there is a chemical inflammatory response. The pH of the trigger point milieu is low, about pH 5. This is in keeping with the findings that the trigger point is hypoxic and ischemic, and therefore acidic. The trigger point has a unique electromyographic feature of persistent, low-amplitude, high frequency discharges that look like endplate potentials. The taut band conducts energy faster than the surrounding muscle tissue does because it is stiffer. The taut band can also be visualized using high definition ultrasonograpy. Clinical diagnosis of a MPS is made by history and by palpation of muscle to identify the taut band. Predisposing and perpetuating factors such as iron insufficiency, vitamin D deficiency, and chronic pelvic pain are considered and addressed if found. The goal is to eliminate the trigger points, reverse trigger point-induced weakness and incoordination, and restore normal muscle function. Manual trigger point releases, and needling the trigger point, without or with local anesthetic, and use of low-level laser are effective ways of inactivating trigger points and reducing pain. MPSs can mimic or cause many common conditions such as chronic daily headache and pelvic pain because of the pain referral patterns of the trigger points.

2.1 Introduction

Muscle pain is a common problem that is underappreciated and often undertreated. Myofascial pain syndrome (MPS) is a myalgic condition in which muscle and musculotendinous pain are the primary symptoms. The heart of the syndrome is the *myofascial trigger point*. The trigger point is a small, painful, locus of abnormal muscle which is the source of the muscular dysfunction. Current thinking about MPS is that a small region within the muscle harbors multiple foci of trigger points, more accurately called trigger zones, which generate pain. The trigger point itself is a *tender region in a taut band* in skeletal muscle (Simons et al. 1999). The taut band is formed by a group of contracted muscle fibers, and is readily palpable. There may be a degree of nodularity in the taut band, particularly at the region of greatest hardness, which is also usually the region of greatest tenderness. However, nodularity is by no means always palpable, and is certainly not required for the identification of the trigger point. Tenderness is usually greatest at the region of maximal hardness or greatest resistance to palpation. Andrew Fischer measured the stiffness of the taut band with a compliance meter, emphasizing the hardness of the

discrete band of muscle that harbors the tender region (Fischer 1987). Thus, *the trigger point is a focus of sensory hyperirritability on a discrete, hyperactive region of muscle*.

2.1.1 Trigger Point Manifestations

The trigger point is responsible for the clinical symptoms of MPS (Table 2.1). *Local tenderness* is quintessential to the trigger point. *Pain at a distance* is characteristic of MPS. It represents *referred pain* that is the result of trigger point-induced central sensitization. Nociceptive activity that arises in foci of painful muscle activates spinal cord dorsal horn neurons and sensitizes the central nervous system, causing *central sensitization, hyperalgesia, and referred pain. Muscle weakness* without atrophy occurs due to trigger point induced motor inhibition. *Restricted range of motion* occurs because of the shortening of the contracted taut band, and perhaps because of pain. The range of motion of hypermobile individuals must be interpreted cautiously, because it can appear to be normal, but can still be restricted for such an individual. *Impaired reciprocal inhibition* results in cocontraction of agonists and antagonists, thus interfering with fine motor control and coordination. *Autonomic disturbances* can accompany trigger point activation, leading to changes in skin temperature and color, piloerection (goosebumps), and lacrimation.

2.1.2 Trigger Point Pain

The trigger point causes pain. At its most activated state, it causes pain at rest. Less severe, it causes pain as the muscle is used. Such trigger points that cause spontaneous pain are called *active trigger points*. A trigger point that is not spontaneously painful with use or at rest is termed *latent*; it is recognized by a taut band in the muscle. It does not reproduce the patient's usual pain, but is painful when activated by mechanical stimulation such as palpation or needling (Simons et al. 1999). This descriptive terminology illustrates the dynamic nature of the trigger point, changing in its degree of irritability or activity, and raising the question of what the minimum

Table 2.1 Myofascial trigger point features

Motor	Sensory
Taut band	Localized pain
Twitch response	Referred pain
Weakness without atrophy	Central sensitization
Loss of reciprocal inhibition	Peripheral sensitization
Electromyographic endplate noise	Subject to sympathetic modulation
Subject to sympathetic modulation	

changes are that occur in muscle when it is injured or stressed to form the nascent trigger point. The clinically evident progression from a nontender taut band to a tender taut band suggests that the first change in muscle is the development of the contracted or taut group of muscle fibers that can then become painful when sufficiently stressed.

Myofascial pain from trigger points is extremely common as a cause of acute muscle pain and of chronic pain. It is a cause of acute backache, tension-type headache, shoulder pain, tennis elbow, pelvic floor pain, and levator ani syndrome, and many other different presentations. It has long been overlooked because many practitioners lack the ability to examine skeletal muscle well enough to detect the localized hardness or taut muscle bands characteristic of myofascial trigger points (MTrPs). Once diagnosed by physical examination, a treatment plan can be developed to inactivate the trigger points and to minimize their tendency to recur. This chapter will present the current concepts of MTrP formation, how trigger points cause pain, how they are diagnosed, and how they are treated. The chapter will close with descriptions of some specific clinical MPSs.

2.1.3 Current State of Knowledge

Knowledge and understanding about MPS has progressed from the stage of classical clinical descriptions of local trigger point manifestations and referred pain symptoms to sophisticated descriptions of the biochemistry of the trigger point region by microdialysis, the imaging of the trigger point taut band by specific magnetic resonance imaging techniques, and explorations of the cerebral responses to trigger point activation. Current and ongoing studies are underway to better define the role of MTrPs in clinical syndromes such as tension-type and migraine headache. This chapter will detail the basic concepts of the MTrP which is the central feature of the MPS, and then evaluate the current state myofascial pain studies.

We owe our present awareness of myofascial pain as an important clinical entity to the work of Janet G. Travell (1901–1997), and later to the incredibly productive collaboration between Dr. Travell and Dr. David G. Simons (Travell and Simons 1983, 1992). Dr. Travell took the landmark studies of Kellgren (1938a, b, 1949) which described the referred pain patterns resulting from injection of hypertonic saline into muscle and other tissues, and the resolution of referred pain by injection of local anesthetic (Kellgren 1938b), and applied them to what were then considered enigmatic clinical syndromes, beginning with noncardiac chest pain that persisted after myocardial infarction (Travell and Rinzler 1952). She mapped the referred pain patterns resulting from muscle pain arising in many different areas in the body (Travell and Rinzler 1952), and described a system of treatment that involved inactivation of the regions of localized muscle soreness through the use of vapocoolant spray and stretch, and injection of procaine, a local anesthetic. She used the term “myofascial” to describe the involvement of both muscle and its

covering tissue, the fascia, and "trigger point" to convey the notion that pain initiated at one site in a particular muscle triggered pain felt at a site distant to the point of origin. Previous descriptions of muscle pain, which most probably referred to what we now call MTrPs are known, but were never developed systematically into a body of knowledge in the way that Janet Travell did with her collaborators, most notably David Simons.

2.2 Clinical Presentation

MPS presents both as acute and chronic muscle pain. In both cases, muscle pain is like other somatic and visceral pains, dull, aching, and poorly localized. Unlike cutaneous pain which is sharp and precisely localized, muscle pain is rarely sharp and stabbing, though it can be, for example, as a stabbing headache pain. It is most often felt as a deep, aching pain, but it can mimic other pains such as radicular pain or visceral pain. It may be accompanied by a sensory component of paresthesias or dysesthesias. MPSs can be enigmatic, because pain may be felt elsewhere than where the pain originates. MPS may persist long after the initiating cause of pain has resolved, as in late MPS persisting months or years after whiplash injury. It may be further complicated by nerve entrapments caused by constricting myofascial taut bands. Thus, MPS can be complex, with the underlying cause not obvious. It may be more straightforward, especially when it is acute or subacute.

2.3 Definition

MPS is pain of muscular origin that arises from MTrPs. In this way it is differentiated from painful, inflammatory myositis and from fibromyalgia which is defined as chronic, widespread pain associated with muscle tenderness, but not with trigger points. The central feature of the MPS is the *MTrP*.

2.3.1 Primary Trigger Point Characteristics

The *trigger poin*t has both a sensory and a motor abnormality. It is comprised of an abnormal muscle structure, the taut band, and an associated sensory alteration, pain (Fig. 2.1). The taut band is a localized, usually linear, band of hardened muscle. The contracted muscle band of the trigger point is discrete within the muscle, and does not involve the entire muscle. Thus, trigger point-containing muscle has a heterogeneous feel of hard and soft areas, rather than a homogeneous uniform consistency. The current model of the taut band is that it is made up of a series of

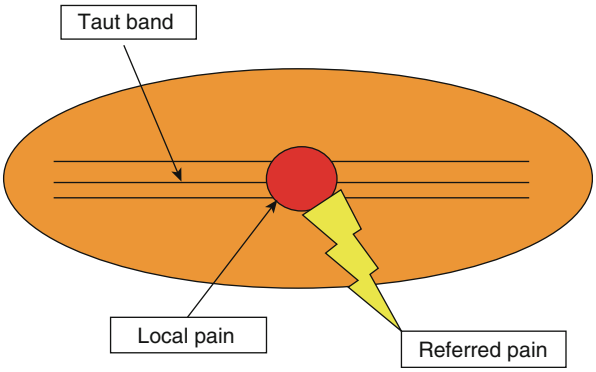


Fig. 2.1 The trigger point contains a band of hardened muscle, which may have a nodular component as well. The hardened band is known as a taut band. It extends partially or wholly between the tendinous insertions of the muscle. The region of greatest hardness is usually the zone of greatest tenderness. The notable feature of the trigger point, especially the active trigger point that is associated with the patient's pain, is the feature of referred pain. Thus, stimulating the tender area of a taut band in the upper trapezius muscle may elicit pain in the ipsilateral temple and cause headache

contracted muscle fibers, made up of multiple foci of intensely contracted sarcomeres thought to be located at or near the motor endplate zone (Fig. 2.2). The intense contraction of the trigger point results in a sensory phenomenon of localized, exquisite pain that is always associated with the taut band. Pain can also be elicited by mechanical stimulation of the taut band (Table 2.1). Trigger points are categorized as active or latent, depending on whether they spontaneously produce pain (an active trigger point), or produce pain only on mechanical stimulation of the trigger point, like palpation, (a latent trigger point). A most important characteristic of the active trigger point is referred pain that is initiated by the trigger point. This property has made diagnosis more difficult because pain may be felt at a distance far from its origin. Referred pain makes the diagnostic process more complex, because the cause of the pain is not necessarily close to where the pain is felt. Sacroiliac joint pain, for example, can originate in the thoracolumbar deep paraspinal muscles, the multifidi. Arm and hand pain can originate in neck or shoulder muscles (Fig. 2.3). Thus, the clinician must be aware of referred pain patterns and be familiar with the muscles that can cause pain to be felt in a certain distribution of the body. Referred pain is a characteristic of spread of nociceptive activation in the central nervous system, specifically in the spinal cord (see Sect. 2.8.2).

2.3.2 Additional Trigger Point Characteristics

The trigger point has other characteristics in addition to the taut band and pain. Among the motor phenomena associated with the trigger point is a *local twitch*

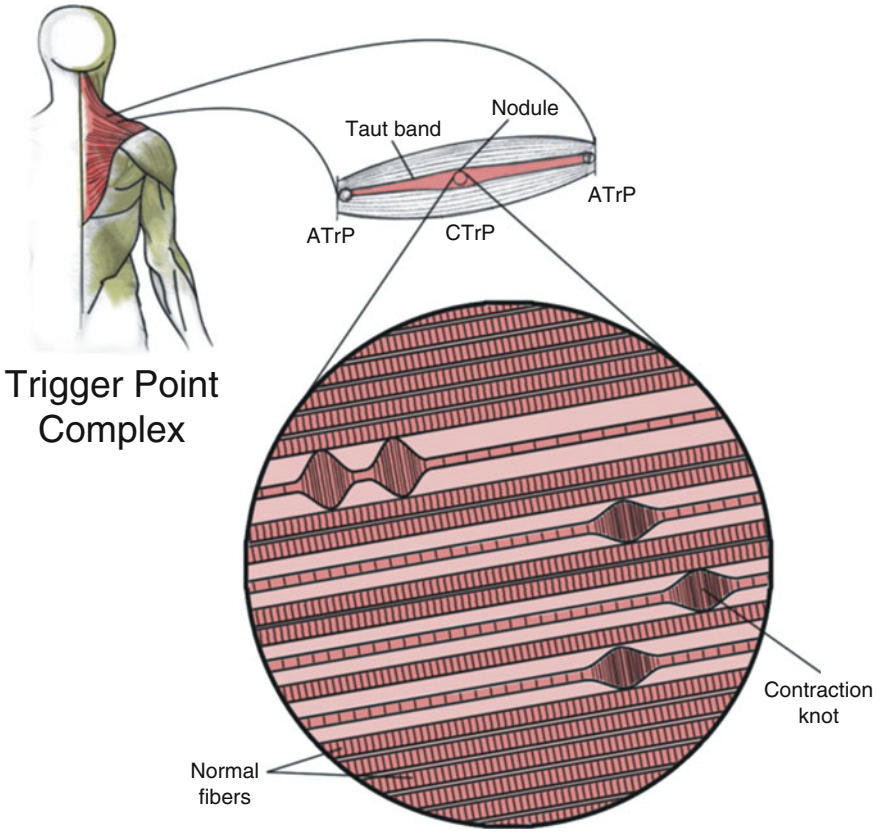


Fig. 2.2 The trigger point is thought to be made up of a number of muscle fibers that contain focal areas of intensely contracted sarcomeres, as illustrated in this diagram. These focal areas of small swellings are called contraction knots. They have not been demonstrated in muscle taken from trigger points in humans, and remain theoretical, but contraction knots do fit in with the information about trigger points gained from studies in humans, including the high-frequency spontaneous electrical activity seen in trigger point electromyograms. Shah et al. (2008), used with permission

response that is elicited by mechanical stimulation. The twitch response is a local contraction of the taut band alone, elicited either by manual means of a strumming palpation, or by intramuscular stimulation with a needle. It is differentiated from a golgi tendon reflex which involves contraction of an entire muscle in response to stretch. A twitch response that is obtained by needling is best elicited with the needle at the trigger point zone (Hong 1994; Hong and Torigoe 1994; Hong and Yu 1998). It is a brief (25–250 ms), high-amplitude, polyphasic electrical discharge. Needle stimulation away from the taut band or trigger spot produces an attenuated electromyographic discharge. The twitch response is dependent on an intact spinal cord reflex arc. Severing the peripheral nerve completely abolishes the local twitch response, whereas transecting the spinal cord does not abolish the twitch response

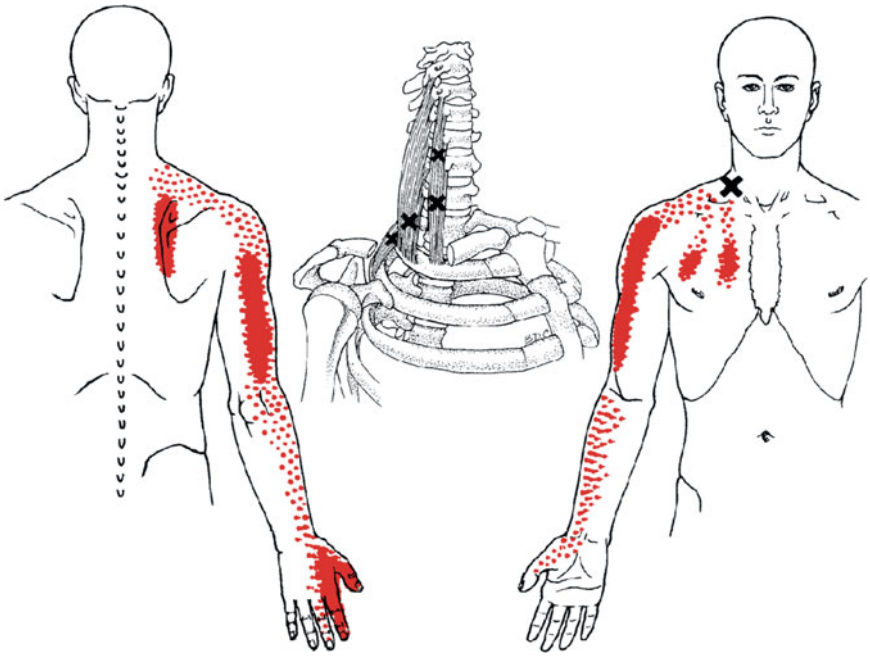


Fig. 2.3 Trigger points in the medial and anterior scalene muscles refer pain to the anterior chest, the upper back in the distribution of the dorsal scapular nerve, and into the ipsilateral arm. The referral pattern is segmental, largely in the distribution of the fifth cervical nerve root dermatome and myotome, with spillover into the adjacent root distributions. Mediclip CD ROM (1996) Lippincott Williams & Wilkins, used with permission

(Hong 1994; Hong et al. 1995). Thus, the local twitch response is mediated through the spinal cord, and is not affected by supraspinal influences. The twitch response is unique to the trigger point, and is not seen in normal muscle.

2.3.3 Trigger Point Identification

Identification of the taut band is now possible with a number of objective techniques. The taut band and the twitch response can be visualized by ultrasound (Gerwin and Duranleau 1997; Sikdar et al. 2008). Newer ultrasound devices produce high-resolution images of the taut band, as noted below, and may be useful in future research studies of the trigger point. Magnetic resonance elastography is another new technique that can differentiate tissues of varying densities. The technique involves the introduction of cyclic waves into the muscle, and then using phase contrast imaging to identify tissue distortions. Shear waves travel more rapidly in stiffer tissues. The harder taut band can be distinguished from the surrounding normal muscle by this technique (Chen et al. 2007, 2008). MR elastography will probably emerge as an effective tool for the identification of the trigger point taut band.

The combination of vibration sonoelastography with ultrasound imaging can localize hypoechoeic, elliptically shaped, focal areas that correspond with the location of a palpable trigger point nodule in the trapezius muscle (Sikdar et al. 2008). This technique can be used to image MTrPs clinically, as well as to identify them and follow them in research studies.

Thus, there are now a number of ways in which trigger points can be imaged objectively for both clinical and research purposes. The practical application of these approaches is just beginning to be explored, but it is likely that within the decade there will be readily more available techniques to confirm the presence of at least the taut band of the trigger point.

2.3.4 Weakness

Muscles harboring a trigger point are often weak. Weakness in affected muscles occurs without atrophy, and is not neuropathic or myopathic in the sense that weakness is not caused by either a neuropathy or a myopathy or myositis (Simons et al. 1999 p. 109). It is usually rapidly reversible immediately on inactivation of the trigger point, suggesting that it is caused by inhibition of muscle action. One mechanism that has been postulated is that muscle contraction is simply limited to a degree below the threshold that can activate pain. However, a trigger point in one muscle can inhibit effort or contractile force in another muscle, suggesting a role for central motor inhibition. However, there is a paucity of studies looking at the nature of weakness in myofascial pain.

2.3.5 Recruitment

The trigger point causes a disordered recruitment of muscles that work together to produce an action. For example, the orderly activation of muscles that produces abduction of the upper extremity is disrupted by a latent trigger point, and is restored by inactivation of the latent trigger point (Lucas et al. 2004, 2007). Likewise, the ability to rapidly activate painful and pain-free synergistic muscles is more severely impaired in women with chronic trapezius myalgia (TM), in which there are active and latent trigger points, than is the ability to produce maximal muscle activation (Andersen et al. 2008a, b).

2.3.6 Reciprocal Inhibition

Reciprocal inhibition, whereby contraction of one muscle is inhibited by the contraction of its antagonist muscle, is reduced or absent when the activated muscle

contains a trigger point. Lack of reciprocal inhibition causes cocontraction that reduces the quality of movement and leads to clumsiness and an incoordination of fine movement.

2.3.7 Range of Motion

Range of motion around a joint moved by muscles with trigger points is often limited. The end range may be painful, but limitation of the range may be painless unless the patient is pushed to move beyond comfort. Limitation of range of motion is not a reliable indicator of the presence of a trigger point in persons who are hypermobile, because their range can be limited and yet still be within the usual range of motion for the general population.

2.3.8 Functional Adaptation

Functional adaptation of muscle action occurs when there is muscle pain. An active trigger point is a source of localized muscle pain. Experimental muscle pain induced by injection of hypertonic saline into the trapezius muscle causes a short-term dynamic reorganization of the spatial distribution of muscle activity (Madeleine et al. 2006). Changes in spatial distribution also occur with muscle contraction, the changes correlating with the duration of contraction (Farina et al. 2008). This suggests that a more long-lasting nociceptive irritant like a trigger point would also cause a functional spatial reorganization of muscle activity, although this has never been studied.

2.4 Sensory Changes

The sensory change associated with the trigger point is pain, local, referred, and hypersensitive. It can be acute or it can be chronic. It is specifically associated with the MTrP taut band. The trigger point is a *tender focus in muscle*, the region of tenderness always located on the taut band. The region of greatest hardness is usually also the region of greatest tenderness. A tender trigger point always means that there is hyperalgesia or allodynia (For details see Chaps. 3 and 4 in the companion volume by Mense and Gerwin (2010)). Pain at the trigger point is due to the release of neuropeptides, cytokines, and inflammatory substances such as substance P, calcitonin gene-related peptide (CGRP), IL-1α, and bradykinin (Shah et al. 2005; Mense 2009), and protons which create local acidity, plus other factors which will be discussed below. Models for *acute muscle pain* have been developed and have yielded information about the generation of local and referred pain (Mense and Hoheisel 2008; Mense 1993; Graven-Nielsen and Mense 2001;

Hoheisel et al. 2004; Sluka et al. 2003; Kuan et al. 2007a, b; Lambertz et al. 2008; Taguchi et al. 2008). However, most clinically relevant muscular pain syndromes last far longer than the conditions studied in animals or even in humans studied under laboratory conditions. Therefore, there is great interest in studying longer-lasting and chronic pain in humans.

When pain occurs only with mechanical stimulation of the trigger point, either by the application of pressure or by needling, the trigger point is termed a *latent trigger point***.** The fact that a trigger point does not cause spontaneous pain (latent) does not mean that it is clinically irrelevant with respect to pain. The trigger point is a dynamic, not static, entity, meaning that it can undergo transitions between a nontender taut band to a latent trigger point to an active trigger point and back again (Chen et al. 2000). The latent trigger point is hypersensitive to the injection of the known nociceptive activators hypertonic saline and glutamate. In addition, the latent trigger point also has an increased response, with referred pain, to the injection of the non-nociceptive activator isotonic saline, indicating that latent trigger points have both a nociceptive hypersensitivity and a non-nociceptive hypersensitivity (allodynia) not seen in nontrigger point regions (Li et al. 2009).

A nontender taut band is not included in trigger point nomenclature, although it is in all likelihood the first, as well as the necessary, component of the trigger point.

Up to this point, only the local tenderness of the trigger point has been discussed. However, a key feature of the trigger point is the presence of referred pain, which is a manifestation of central sensitization. Central sensitization (discussed in Chap. 4 in the companion volume by Mense and Gerwin (2010)) results in a spread of perceived pain to distant and larger areas of the body than just the local tenderness found at the taut band.

2.5 Electrophysiology of the Trigger Point: Spontaneous Electrical Activity (Endplate Noise)

The trigger point in resting muscle had long been considered to be electrically silent. No motor action potential has been associated with the trigger point or the taut band in resting muscle (Simons et al. 1999). Hubbard and Berkoff (1993) published the first report of persistent, low-amplitude, high-frequency discharges found at the trigger point region in active trigger points (Fig. 2.4). This activity, which initially came to be known as spontaneous electrical activity (SEA), is associated with the trigger point region (Simons et al. 1995; Hong and Simons 1998). As the electrode is moved away from the trigger zone, the SEA diminishes. Likewise, the SEA diminishes as the needle is placed outside the taut band (Hong and Torigoe 1994). A needle placed 1 cm away from the trigger zone and outside the taut band does not display SEA (Hubbard and Berkoff 1993).

The electrical activity associated with the trigger point is thought to arise from the motor endplate (Simons et al. 1999), and has been named endplate noise by Simons (2001). There has been some controversy about the nature of this electrical

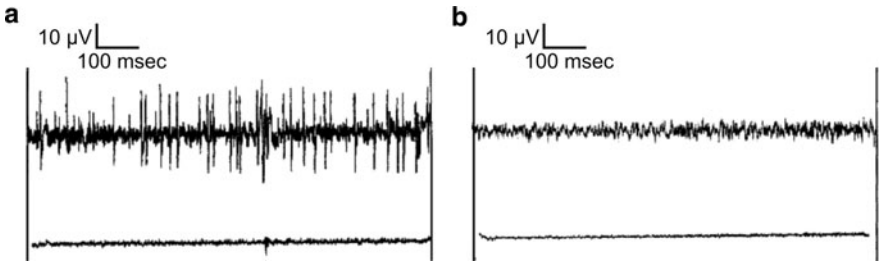


Fig. 2.4 **(a)** Shows the high-frequency, spontaneous, low amplitude electrical activity of 50 μV or less, punctuated by high amplitude discharges of up to several hundred microvolts in the active trigger point, which are characteristic of the trigger point. The adjacent muscle that is not part of the taut band is electrically silent. **(b)** Shows the effect of systemic phentolamine, an alpha-adrenergic inhibitor, demonstrating the degree to which inhibition of sympathetic activity can modulate the spontaneous electrical activity of the trigger point. Chen et al. (1998), used with permission

activity, but the low-amplitude, rather constant waveforms are consistent with the small, monophasic negative waveform of <50 μV called miniature endplate potentials (MEPPs) and the higher-amplitude waveforms seen only in active trigger point zones are consistent with endplate spikes (Dumitru et al. 1998). MEPPs are thought to be the result of spontaneous release of acetylcholine from motor nerve potentials. Botulinum toxin reduces the endplate noise in rabbit MTrPs, supporting the postulated role of acetylcholine release from the motor nerve terminal in the generation of endplate noise (Kuan et al. 2002). The current flow associated with opening of sodium and potassium channels is detected by extracellular needle electrodes at about 10% of the amplitude of intracellular micropipette recording electrodes. The low-amplitude activity is thought to be the result of the release of acetylcholine sufficient only to generate subthreshold endplate depolarization in close proximity to the electrode. The endplate spike of several hundred microvolt amplitude represents temporally summated miniature endplate potentials sufficient to reach or exceed the membrane threshold value (Dumitru et al. 1998). The studies by Hubbard and Berkoff (1993) and subsequently others compared the SEA at the trigger zone with a control point a centimeter or so away from the index electrode. The absence of electrical activity at the control electrode confirms the lack of anterior horn cell motor action potentials and therefore establishes the resting state of the muscle. However, it does not guarantee that the activity at the trigger zone is abnormal. The endplate noise was, however, 5 times more frequent in endplate zones in the trigger zone than in endplate zones outside the trigger zone and the taut band (Simons et al. 1995). These active zones are similar to the active sites with endplate spike activity reported by Partanen (1999). Partanen, however, in contrast to Dumitru and to Simons, believed that this activity came from endplates associated with the intrafusal fibers of muscle spindles, largely because this activity was found outside of the endplate zone (Partanen 1999). However, it is now clear that motor endplates are more widely distributed throughout the muscle than in just the endplate zone.

Endplate noise intensity is directly correlated with the degree of trigger point irritability as measured by PPT (Kuan et al. 2007b). Thus, motor endplate activity is greater in active, spontaneously painful trigger points than in latent trigger points. Greater endplate activity and consequently greater focal muscle sarcomere compression can be thought of as being associated with greater local muscle injury and local release of nociceptive substances.

2.6 Etiology of Myofascial Trigger Points

2.6.1 Generation of the Taut Band

The cause of trigger points is a matter of speculation. It appears evident from clinical inspection that trigger points form as latent trigger points first and then become tender as muscle is activated. This sequence of events is assumed because latent trigger points exist without spontaneous pain. Furthermore, trigger point tenderness does not occur except in regions of muscle hardness, but regions of muscle hardness occur without local or referred pain. Hence, it is concluded that muscle hardness or the taut band that occurs in the absence of pain is the first abnormality, and that the active trigger point is a more activated or secondary stage of the trigger point. However, this sequence of events, as simple as it is, has not been systematically studied and confirmed.

2.6.2 Muscle Overuse Syndromes and Myofascial Pain Syndrome

Current thinking, in keeping with the Expanded Integrated Hypothesis of the Trigger Point (Gerwin et al. 2004; Simons et al. 1999 pp. 69–78; Gerwin 2008), is that localized ischemia is associated with the acute development of the trigger point and with its maintenance. Localized ischemia represents capillary compression resulting from forces generated within the taut band. In turn, the release of vasodilating substances such as CGRP and Substance P lead to localized noninflammatory edema that further compresses capillaries and contributes to ongoing ischemia.

2.6.3 The Neuromuscular Junction: The Role of the Neuromuscular Junction in Trigger Point Formation

Trigger point pain does not occur in the absence of a taut band, as stated above. The mechanism of local and referred pain is well understood as a general phenomenon, based on the release of local neurotransmitters, hydrogen ions, potassium ions, and cytokines peripherally, and the activation of nociceptive neurons in the dorsal horn

centrally. The spread of nociceptive neuronal activation segmentally is also a well-described phenomenon, regardless of the tissue of origin. However, the initial change in muscle associated with the trigger point seems to be a motor abnormality, the development of the taut band. The mechanism of taut band development remains a matter of speculation, and has not been proven. Simons' Integrated Hypothesis of the Trigger Point (Simons et al. 1999), expanded on by Gerwin et al. (2004), and by Gerwin (2008), suggests that an excess of acetylcholine at the motor endplate, modulated by adrenergic modulation of neurotransmitter release, inhibition of acetylcholine esterase, and other modulating factors such as adenosine concentration, and by feedback control of neurotransmitter release related to endplate discharge frequency, results in the development of localized muscle contraction. This is supported by the initial observations by Hubbard and Berkoff (1993) of spontaneous low-amplitude electrical activity at the trigger point site, later called "endplate noise" by Simons. This activity is modulated by an alpha-adrenergic blocking agent (Chen et al. 1998) and by botulinum toxin (Kuan et al. 2002), indicating that it is subject to sympathetic nervous system influences, and is also dependent on acetylcholine release. The role of sympathetic modulation of the SEA is a most important concept, because of the important role that the sympathetic nervous system plays in maintaining the abnormal electrical activity at the trigger point. A postsynaptic muscle dysfunction that increases intracellular calcium concentration through a leaky Ryanodine receptor calcium channel on the sarcoplasmic reticulum membrane, or through adrenergic-mediated second-messenger systems involving protein kinase C and cyclic-AMP, initiating actin–myosin interaction, may also result in muscle fibril contraction, and is an additional consideration for the development of persistent contraction (Gerwin 2008). Similar considerations were discussed by McPartland and Simons (2006) in discussing possible molecular mechanisms of trigger point formation. The role of calcium in the SEA associated with the trigger zone was examined using verapamil as a calcium channel blocker in the rabbit model (Hou et al. 2002). SEA was significantly inhibited using verapamil, indicating that calcium channel activity is important in the generation of trigger point endplate noise. Mense et al. (2003) have also explored inhibition of acetylcholine esterase as a mechanism of trigger point generation.

The association of endplate noise and the trigger zone has led to the suggestion that the trigger zone is where the endplate zone is located and that is in mid-belly of the muscle. However, the muscle mid-belly is not always obvious and depends on the specific anatomy of the muscle. In addition, the layout of individual muscle fibers may be complex. The sartorius muscle, for example, the longest muscle in the human body, has some muscle fibers that run the entire length of the muscle and others that end within muscle fascicles. The endplate zone innervating motor units is not necessarily near the fiber midpoint (Harris et al. 2005). The implication for muscle is that the full extent of the muscle must be examined for taut bands and tenderness. Finding trigger points eccentrically located in the muscle does not negate the concept of dysfunctional motor endplates as a significant factor in trigger point genesis.

The muscle endplate region of the neuromuscular junction is considered to be the domain of the physiological dysfunction leading to trigger point development. The observation that muscle nociceptor density is higher in endplate zones (Qerama et al. 2004, 2005) is consistent with this hypothesis.

2.6.4 *Peripheral Nerve Sensitization in Myofascial Pain Syndrome*

Peripheral nerve sensitization is well-recognized in chronic pain syndromes (see also Chap. 3 in the companion volume by Mense and Gerwin (2010)). It has not been addressed in MPSs where emphasis has been placed more on changes in muscle than in nerve. Nevertheless, it would seem reasonable that peripheral nerve sensitization is a consequence of chronic myofascial pain just as in other chronic pain syndromes. Some neural manifestations of the MTrP are clearly related to a spinal reflex, such as the local twitch reflex (Hong et al. 1995). Other studies have suggested that there is central integration at the spinal cord level in animal trigger point models (Kuan et al. 2007a). The role of the peripheral nerve at the neuromuscular junction and its relationship to anterior horn cell function in MPS, however, have been little studied.

One study of neural alteration in MPS showed that neuromuscular jitter by stimulated single fiber electromyography has a significantly increased mean consecutive difference (jitter) in the trapezius and levator scapulae muscles in subjects with MPS compared to controls (Chang et al. 2008). The instability of peripheral endplate function could be related to (1) peripheral motor nerve axonal degeneration and regeneration, or (2) motor neuron degeneration with development of collateral reinnervation. This means that the MTrP has a complex peripheral and/or central motor dysfunction as well as a sensory abnormality with peripheral and/or central hypersensitization.

2.6.5 *Hypoxia and Ischemia*

The myofascial trigger zone or region is hypoxic, consistent with the concept that there is capillary compression and ischemia. Ischemia and hypoxia are inevitably connected. There is a region of severe oxygen desaturation at the presumed core, surrounded by a region of increased oxygenation, as if the core were ischemic and surrounded by a hyperemic zone (Brückle et al. 1990). Likewise, temperature studies of the trigger zone reported by Travell (1954), showed an increase in temperature in the trigger point region. This would be consistent with a hyperemic area surrounding the trigger zone, but inconsistent with a hypoxic trigger zone core. Infrared studies of the skin overlying muscles affected by trigger points were done

in the 1980s and 1990s, with varying results (Pogrel et al. 1996, Radhakrishna and Burnham 2001), but address only the peri-trigger point tissue, and not the core of the trigger point itself.

2.6.6 *Biochemistry of the Trigger Point Region*

Biochemical changes in the area of the trigger point have been identified by Shah et al. (2005) through studies of the trigger point region by microdialysis. In their experiments, Shah et al. placed a microdialysis probe in the trigger point region of active trigger points, and advanced it slowly until a twitch response was obtained, signifying that the probe had reached the trigger point zone. Elevations of substance P, CGRP, bradykinin, serotonin, and cytokines are found in active trigger point milieu relative to the concentrations of these substances in latent trigger point regions and in normal muscle (Fig. 2.5; Shah et al. 2005). As the probe advanced toward the trigger point, the concentrations of a number of substances increased, until the twitch occurred and the concentration of these substances fell toward the normal range, but then slowly rose to the initial elevated concentrations over 10–15 min. The pH of the trigger point region is low at pH 4–5 compared to a normal pH of 7.4. Thus, the local active trigger point milieu shows increased substance P that can increase capillary leakage causing local edema, and can potentiate peripheral nociceptor activation. Bradykinin is another elevated substance that is a nociceptive receptor potentiator. CGRP, also elevated, is active at both sensory receptors and at the neuromuscular junction. Low pH can reflect ischemia, and can inhibit acetylcholinesterase activity. An increase in cytokine levels correlates with local pain. The concentrations of some of these substances are also elevated at an active trigger point region compared to a nontrigger point region at a distant muscle site. The concentrations of most of these substances are elevated at a nontrigger point region at a distant site in subjects with active trigger points compared to subjects with latent or absent trigger points (Shah et al. 2008). The active trigger point site was the trapezius muscle. The distant site was the gastrocnemius muscle. The pH was lower than normal, and the other analytes such as substance P and various cytokines were elevated to a slight, but definite, degree. Bradykinin was the exception, as it was not elevated in the gastrocnemius muscle when there was an active trigger point in the trapezius muscle. There is no clear explanation for this phenomenon. One possibility is that an active trigger point in one muscle evokes widespread central activation that in turn activates the peripheral receptors. However, it is also possible that the gastrocnemius muscle in a person with an active trigger point in the trapezius muscle is more likely to have latent trigger points that were unknowingly sampled. The ability to sample the interstitial milieu of the trigger point region has great potential for permitting the unraveling of the mechanism of trigger point activity and the generation of pain from muscle (Shah and Gilliams 2008).

Muscle 5-HT and glutamate elevations in trapezius muscle interstitial fluid in women with work-related myalgia correlate directly with pain intensity, while

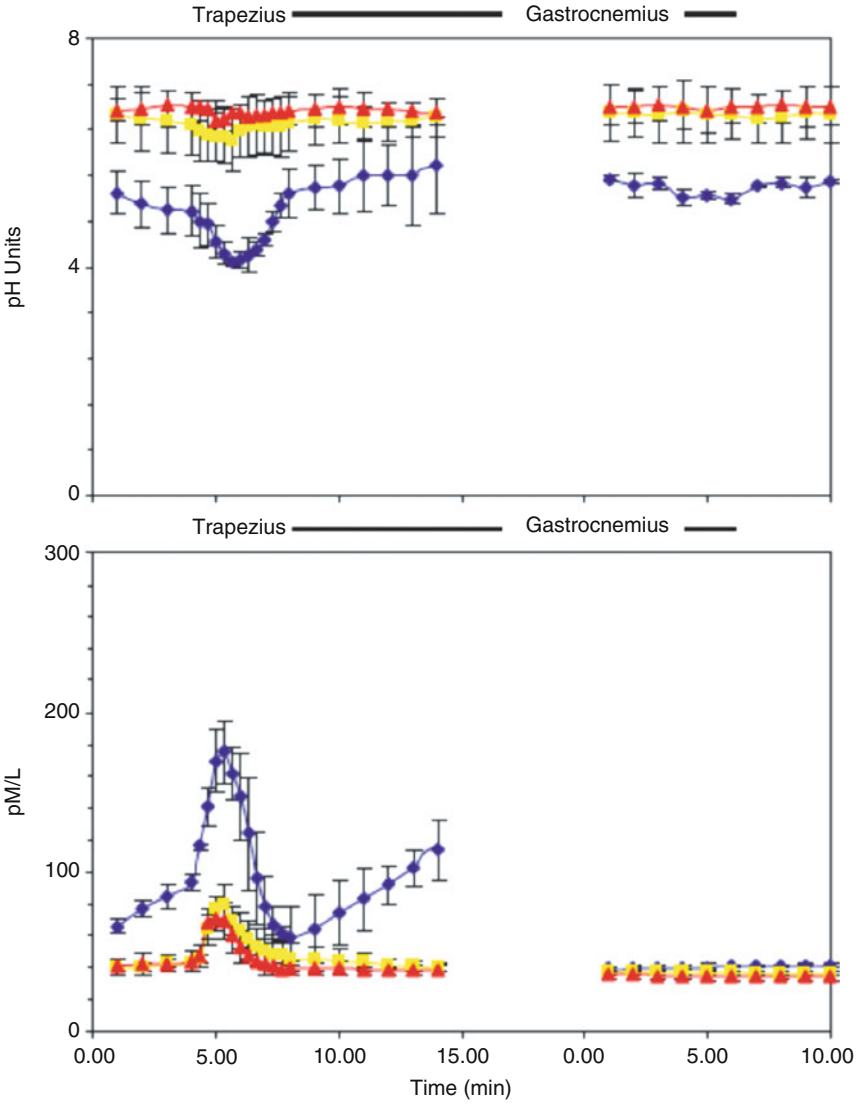


Fig. 2.5 These two graphs show the results of microdialysis of the trigger point milieu in an active trigger point in the upper trapezius, and in normal muscle in the gastrocnemius region. The pH at the trapezius trigger point is lowered (**a**, *left graph*), peaking as the microdialysis needle approaches the trigger zone, and returns toward baseline after the local twitch response is elicited. There is a slight decrease in pH in the gastrocnemius muscle that has no trigger point (**a**, *right graph*). Bradykinin levels are also elevated compared to normals, in the active trigger point in the upper trapezius muscle (**b**, *left graph*). There is no difference between the levels of bradykinin in the gastrocnemius muscle in persons with active or latent trigger points in the trapezius, or in controls. The high levels with peak concentrations just before the local twitch response is elicited are also seen for cytokines, substance P and 5 HT (serotonin). Shah et al. (2008), used with permission

lactate and pyruvate increase after low-force exercise significantly more than in control women (Rosendal et al. 2004). Bradykinin and kallidin, potential algesic kinins, are elevated in the interstitial muscle tissue of the descending portion of the trapezius muscle in women with work-related TM, whiplash associated pain (WAP), and controls (CON) (Gerdle et al. 2008a). Bradykinin and kallidin are increased at rest in TM and WAP and increase with exercise more in these two groups than in CON. Whiplash associated disorder (WAD) subjects had a lower trapezius PPT indicating hypersensitivity, and higher interstitial concentrations of IL-6 and 5-HT (Gerdle et al. 2008b). In the three studies that performed microdialysis on interstitial muscle samples, no attempt was made to place the catheter in a trigger point, but the authors noted that typically "a brief involuntary muscle contraction and change of resistance were perceived when the needle penetrated the fascia and muscle," suggesting that a trigger point local twitch response was elicited. However, it is not known where in the muscle the needle tip was finally placed. Nonetheless, this study both supports the study by Shah et al. (2005) and confirms the relevance of the elevation of kinins in clinical muscle pain syndromes. Tissue IL-1 alpha and beta were elevated in the forearm muscles of rats after 8 weeks of a high-repetition, negligible force activity (Barbe et al. 2008), in keeping with trigger point microdialysis findings, but lacking the specificity of trigger point localization.

The biochemical changes at the trigger zone as described by Shah and his colleagues, referred to above, and the decrease in SEA with phentolamine, an alpha-adrenergic blocking agent, lead to a concept of the trigger point in which muscle injury, induced by acute or chronic muscle overload, leads to persistent muscle fiber contraction — the taut band — and to local and referred pain, modulated by adrenergic activity, as summarized in Figs. 2.6 and 2.7 and in the charts in Figs. 2.8 and 2.9.

2.7 Muscle Pathology

Definitive pathological studies of MTrPs in humans or animals remains to be done. Simons and Stolov (1976) published results of canine muscle trigger point biopsies. A single section showed a muscle fiber with intense sarcomere contraction that Simon later called a "contraction knot" (see also Chap. 3). These were considered to be the result of excessive acetylcholine at the motor end plate, causing intense local contraction (Simon's Integrated Hypothesis of the Trigger Point; Simons et al. 1999, pp. 69–78). Such a clear zone of intense sarcomere contraction has not been convincingly replicated in a definite MTrP. An attempt to produce contraction knots in rat muscle by inhibiting acetylcholinesterase, in order to increase the concentration of acetylcholine at the motor endplate, showed higher numbers of abnormally contracted fibers, torn fibers, and longitudinal stripes (Mense et al. 2003). However, the changes did not look like the "contraction knot" seen in the canine specimen. Jacobsen et al. (1991) looked at quadriceps biopsies in fibromyalgia and chronic myofascial pain patients. They found "rubber band" morphology in both groups,

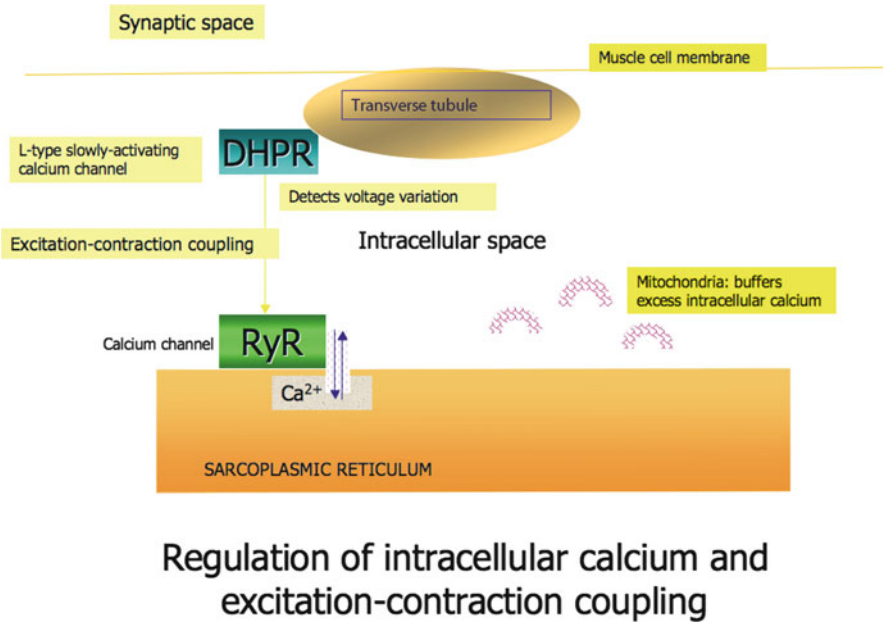


Fig. 2.6 The current concept of the trigger point is that the taut band is the first abnormality, as it is present when there is no pain. The taut band is thought to be the response to a disorder of calcium release in the muscle fiber. Calcium is normally released from the sarcoplasmic reticulum into the cytosol in response to depolarization of the muscle fiber membrane at the motor endplate. Depolarization is detected at the transverse tubule, which then activates the dihydropyridine receptor (DHPR) that in turn opens the ryanodine receptor (RyR) that allows calcium to flow from the sarcoplasmic reticulum, where it is stored, to the cytosol, where it is required for the interaction of actin and myosin that results in muscle contraction. Excessive concentration of acetylcholine at the motor endplate can facilitate an excessive release of calcium from the sarcoplasmic reticulum. A limiting amount of high-energy phosphate bonds (adenosine triphosphate or ATP), as postulated in the "energy crisis" theory of trigger point generation, impairs the reuptake of excessive cytosolic calcium back into the sarcoplasmic reticulum, which normally is required for muscle relaxation

but significantly more in fibromyalgia patients than in myofascial pain patients. The origin of the "rubber band" morphology was not clear, and its relation to "contraction knots" is not clear.

Biopsy studies of nonspecifically painful muscle, but without any intention of sampling a trigger point, have been published. Muscle biopsies performed in 240 subjects with myalgia in one or more muscles, but excluding known causes of muscle pain, including fibromyalgia, showed changes that fell into five different categories (Filosto et al. 2007). The largest group (51.6%) had heterogeneous myopathic changes that were mostly nonspecific. The changes included increased fiber size variation, occasional cell necrosis, some abnormalities of the intermyofibrillar network such as moth-eaten fibers, specific myopathic changes in 6.5%, type I fiber atrophy in 1.6%, and type II B fiber atrophy in 6.5%. Mitochondrial

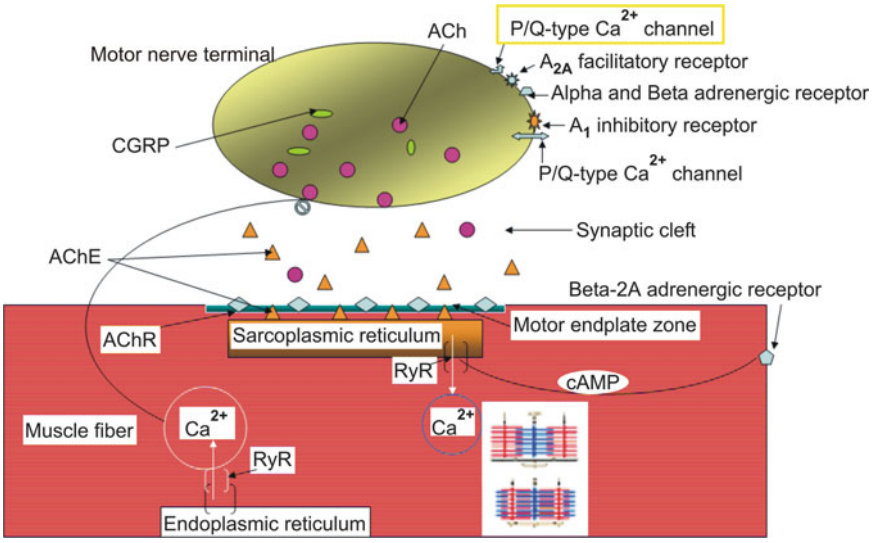


Fig. 2.7 Release of acetylcholine from the motor nerve terminal, the binding of acetylcholine to its endplate region receptor, and the release of calcium into the cytosol to activate muscle contraction, are points where contractile activity can be modulated. Release of acetylcholine from the motor nerve terminal is calcium-dependent, and modulated by adenosine and by sympathetic activity (mediated through alpha and beta adrenergic receptors). Release of acetylcholine is also enhanced by calcitonin gene-related peptide (CGRP). CGRP also up-regulates acetylcholine receptors (AChR), creating more binding sites at the motor endplate, and inhibits acetylcholine esterase (AChE). Sympathetic modulation of cytosolic calcium concentration is also mediated through activation or inhibition of a second messenger system utilizing cyclic adenosine monophosphate (cAMP). A feedback mechanism is also at work in which high cytosolic calcium concentration inhibits release of acetylcholine from the motor nerve terminal. Abbreviations: A_2 and A_{2A} are adenosine receptors, *ACh*: acetylcholine, *AChE*: acetylcholine esterase. *AChR*: acetylcholine receptor, *RyR*: Ryanodine receptor, Ca^{2+}: calcium, *CGRP*: Calcitonin gene-related-peptide

abnormalities were found in 20% of the patients. A third group of 19% had normal biopsies. A neurogenic pattern was found in 7%, and 2.4% had a metabolic myopathy (Filosto et al. 2007). This was a retrospective study, and while it excluded patients with clear causes of myalgia, including patients with fibromyalgia, no comment was made about the presence or absence of myofascial pain. The biopsies were obtained from 1990 to 2003, starting at a time when the diagnosis of myofascial pain was more problematic and questionable in the medical community than it is now. One point of interest is that no case of myoadenylate deaminase deficiency (MADD) was found. MADD is the most common metabolic myopathy. Two other studies published in the 1980s showed changes that are not amenable to inclusion of MPSs. One study looked for specific, diagnostic muscle abnormalities in one third of 109 patients with muscle pain, but the group included a heterogeneous collection of specific conditions that had their own pathological changes (Mills and Edward 1983). No information can be gained from this study about the

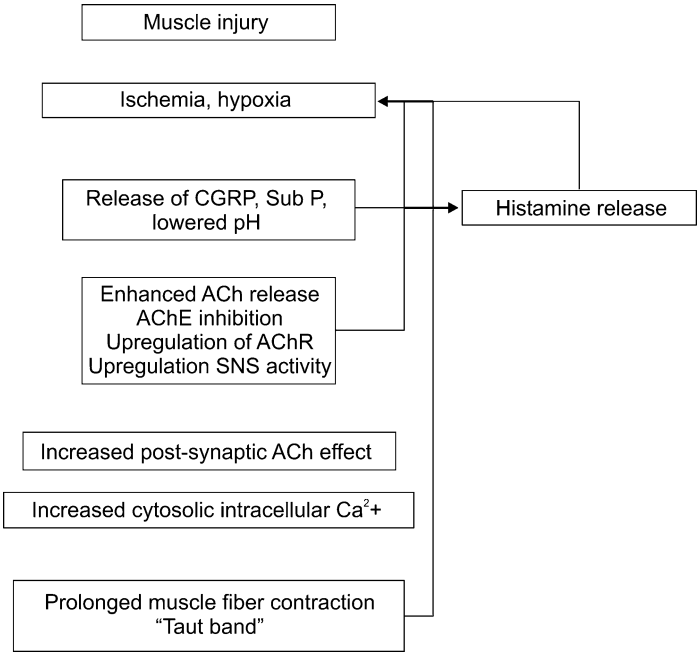


Fig. 2.8 This chart shows the relationship of a muscle injury, such as a single muscle overload or a repetitive overload, to the development of the taut band, the motor abnormality in myofascial pain syndrome. The physiologic changes in this chart cascade downward from muscle injury to ischemia, to release of CRGP and so on, to prolonged muscle fiber contraction and development of the taut band

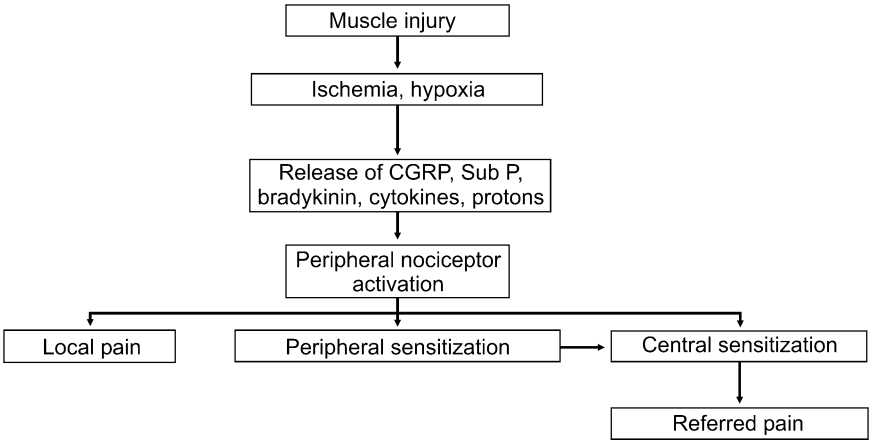


Fig. 2.9 This chart shows the relationship of muscle injury to the sensory manifestations of trigger point pain, namely the activation of peripheral nociceptors and the initiation of central sensitization

pathology of trigger points. The other study of 210 patients showed evidence of "inflammatory myalgias" (polymyositis or polymyalgia rheumatica) in one half of the subjects, and what was called "functional myalgia" of psychological orgin in the other half, which did not show an "organic aetiology" (Serratrice et al. 1980).

There is as yet no unequivocal pathological change that is clearly associated with the trigger point. Intense sarcomere contraction at the trigger point zone remains an attractive hypothesis, but remains to be confirmed pathologically.

2.8 Central Sensitization

2.8.1 Central Pathways

Central connections of the trigger point are of interest because trigger point tenderness is most certainly associated with central sensitization and hypersensitivity, just as is the case with other tissues. This subject is reviewed in this book in Chap. 4 in the companion volume by Mense and Gerwin (2010). There is a central representation of pain that can be imaged with functional magnetic resonance scanning (fMRI) in persons with MTrPs that is consistent with central sensitization. At matched stimulus and pain intensity, significantly enhanced somatosensory and limbic activity and suppressed dorsal hippocampal activity are seen in patients with a hypersensitive MTrP compared to control subjects (Fig. 2.10; Niddam et al. 2007). Modulation of pain evoked from a MTrP by electrical stimulation is centrally mediated through the periaqueductal gray center in the brainstem, as demonstrated by fMRI (Niddam et al. 2008). Supraspinal nociceptive inhibitory pathways are likely to be involved in pain control, and the limbic system in the hippocampus

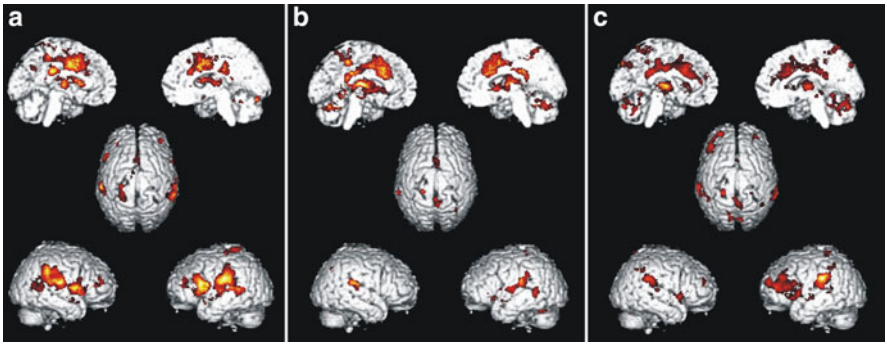


Fig. 2.10 Stimulation of an active trigger point results in enhanced activation of centers in the somatosensory cortex of the brain and the limbic region (insula) (**a**) compared to normal controls (**c**), when stimulation intensity and pain intensity are controlled. Niddam et al. (2007), used with permission

is likely to be involved in the modulation of pain affect, according to the results of these studies. The mechanisms of central sensitization and expansion of dorsal horn reference zones in acute muscle pain have been extensively studied by Mense and his colleagues (Mense 2003). Central sensitization occurs in animal studies with chemically and mechanically induced muscle pain. However, studies in rats do not show a difference in the numbers of neurons in the dorsal horn associated with trigger spots compared to controls (Kuan et al. 2007a, 2007b), indicating that changes occur in individual dorsal horn neurons rather than in the number of neurons activated. Central sensitization is thought to be the mechanism through which referred pain occurs (see Sect. 2.8.2).

2.8.2 Referred Pain

Referred pain is a manifestation of central sensitization of the dorsal horn nociceptive neurons, coupled with convergence of afferent nociceptive fibers on single sensory neurons. As detailed elsewhere in this book (Chaps. 4 and 5 in the companion volume by Mense and Gerwin (2010)), one of the consequences of central sensitization is the activation of otherwise ineffective (sometimes called "sleeping") synaptic connections from one afferent nerve fiber to many recipient nociceptive neurons, thereby expanding the receptive fields of any one specific neuron. The dorsal horn neuron transmits nociceptive impulses rostrally, resulting in activation of the somatosensory cortex. The sensory cortex interprets all input from a dorsal horn neuron as coming from the receptive field of the neuron, which is expanded when the dorsal horn neuron is sensitized. This mechanism can explain the referred pain patterns seen clinically. In addition, the spread of nociceptive afferent fibers extends beyond the one or two segments above and below the level of entry into the dorsal horn of afferent axons carrying classical sensory input such as touch. The wider arborization of incoming nociceptive fibers within the spinal cord increases the spatial distribution of activated dorsal horn neurons sensitized by continuous or recurrent nociceptive input. Thus, the anatomy of nociceptive afferent fibers in the spinal cord may explain some of the more widespread or unusual patterns of referred pain in highly sensitized individuals.

In clinical practice, the most common referred pain distribution patterns are within the same or adjacent spinal segments as the primary sensory nerve. Thus, trigger points in muscles innervated predominantly by C5 nerve root fibers refer pain largely to the C5 dermatome and myotome, overlapping into the C4- and C6-innervated areas. Since muscle innervation is relatively constant, segmental referred pain patterns tend to be relatively constant from one person to another. These patterns have been mapped and recorded, most extensively by Janet Travell, M.D. (Simons et al. 1999). Others have continued to identify and refine trigger point referral patterns (Fig. 2.11) (see for example Hwang et al. 2005a, 2005b).

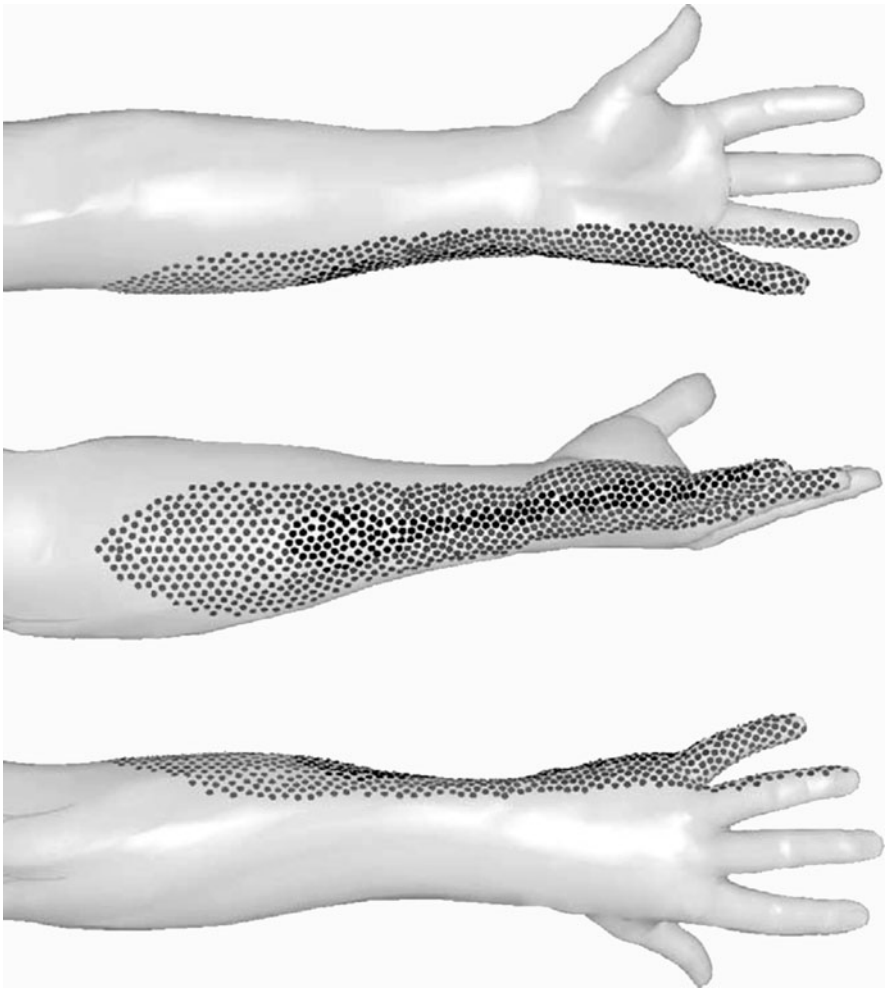


Fig. 2.11 The pronator quadratus muscle refers pain distally to the ulnar (C8) side of the forearm, hand, and fingers. Hwang et al. (2005a), used with permission from IASP

New referred pain patterns have also been described for headache (Fig. 2.12; Fernandez-de-las-Peñas et al. 2005a).

The segmental spread of referred pain may be bilateral. This was noted by Janet Travell for forehead pain caused by trigger points in the clavicular head of the sternocleidomastoid (SCM) muscle (Simons et al. 1999, p. 310). Bilateral forearm referred pain from a unilateral trigger point has also been reported for unilateral epicondylalgia (Fernandez-Carnero et al. 2008). However, in this case it is possible that trigger points may have arisen independently in the contralateral arm through compensatory overuse, or may be present simply because they are so prevalent in

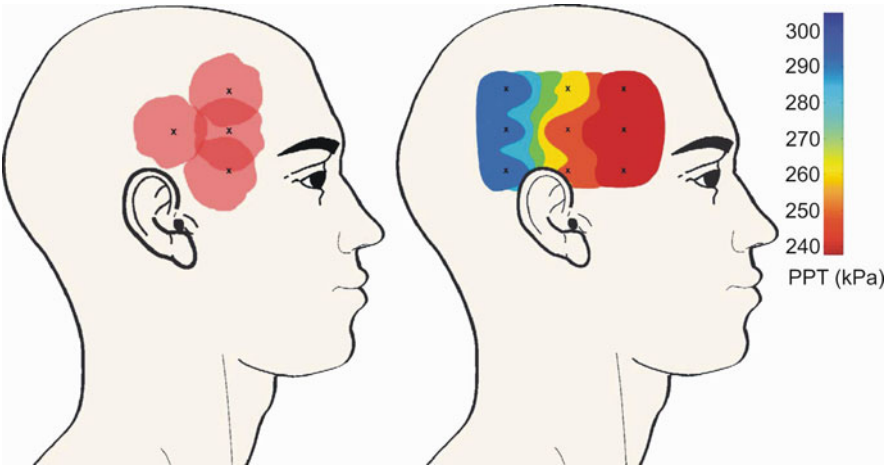


Fig. 2.12 The referred pain pattern of the temporalis muscle. Fernandez-de-las-Peñas et al. (2007b), used with permission

forearm extensor muscles in any case (Gerwin et al. 1997). However, the authors have shown that there is a significant difference in the prevalence of active and latent trigger points in the forearm muscles of subjects with epicondylalgia and control subjects, suggesting that the finding is meaningful.

Central sensitization and widespread pain referral is clinically important. Individuals who have had seemingly local injury wherein pain persists and becomes chronic may develop extraordinary spread of pain, to the extent that pain becomes widespread and hyperalgesia or allodynia may appear to involve most of the body (Fig. 2.13).

2.9 Muscle Stress and Overuse

2.9.1 Muscle Overuse Syndromes

The proposal discussed herein is that muscle overuse, or bio-mechanical stress, is the cause of the trigger point. This concept is central to Simons' Integrated Hypothesis of the trigger point and is expressed by Simons as an energy crisis that he thinks is the primary cause of trigger point phenomena. There are many studies that show that supramaximal muscle contraction or overloaded eccentric contraction can damage muscle and lead to pain, including delayed onset muscle soreness (DOMS) (Mizumura and Taguchi 2008). Repetitive strain is considered a variant of muscle overload, and is thought to have the same effect. A moderate-repetition (nine reaches per minute), high-force (60% of maximum pulling force)

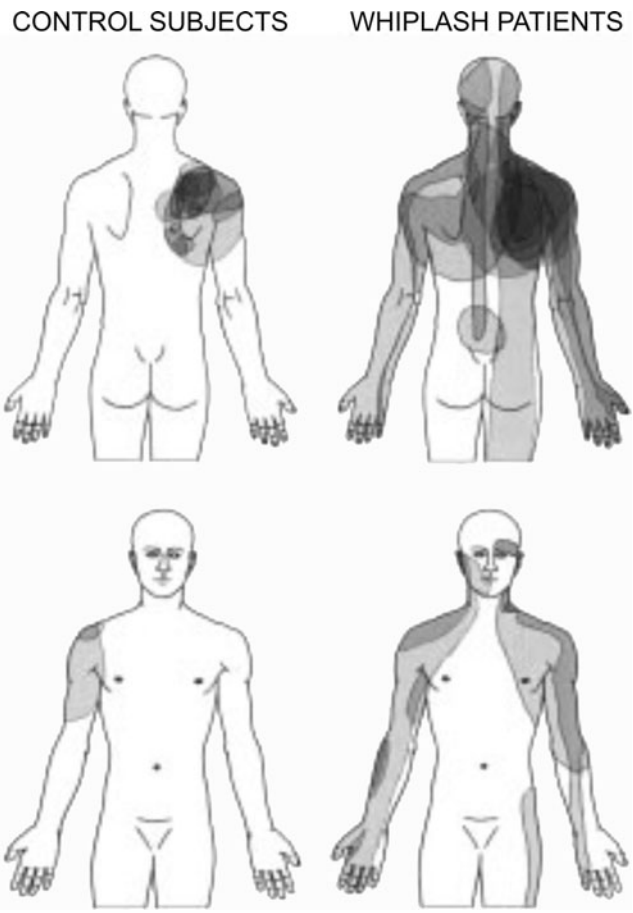


Fig. 2.13 Injection of the infraspinatus muscle with hypertonic saline induces widespread pain in persons with chronic whiplash pain compared to normal controls. The pain is bilateral and extends ventrally, as well as caudally below the waist. Trigger points were not evaluated in this study, but they occur in virtually 100% of individuals with chronic pain after whiplash. This is a striking example of the effect of central sensitization. Johansen et al. (1999), used with permission from IASP

task in rats induces a decrease in motor and nerve function, and signs of central sensitization with mechanical allodynia (Elliott et al. 2009). Maintenance of fixed positions for long periods of time, and sustained contraction of muscle as a result of emotional stress (anxiety, fear, depression), are also thought to produce muscle overuse. There are no studies, however, that show that these phenomena actually lead to the development of the trigger point, although we have postulated that is the case (Gerwin et al. 2004).

Sustained low-level muscle contraction, in contrast to supramaximal contraction, has been implicated in the development of trigger points. The concept is that

the earliest recruited and last deactivated motor units are overworked, particularly during prolonged tasks. This concept has been well summarized by Dommerholt et al. (2006a, b). Support that this is important in the development of MTrPs comes from the studies of Treaster et al. (2006).

The hypothesis that muscle overuse or physical or metabolic stresses lead to muscle dysfunction and pain is based on an underlying assumption, arising from the ischemic, energy-crisis model of the trigger point, that the affected muscle is overworked beyond its capacity to respond without injury (Gerwin et al. 2004). The "Cinderella" hypothesis postulates that a subset of type I muscle fibers is overworked (Hägg 2003), and vulnerable to damage consistent with the energy-crisis model of the trigger point. The finding that type I megafibers are more common in women with TM than in controls (Andersen et al. 2008b) supports the concept that type I muscle fibers are overloaded and injured by repetitive, low-load work (Treaster et al. 2006). Capillary blood supply to the megafibers is poor, suggesting that a local shift to anaerobic metabolism and acidosis has of necessity occurred. These changes are consistent with the "Cinderella" hypothesis of type I muscle fiber overuse. However, fast-twitch type II muscle fibers are more likely to be recruited and injured with eccentric exercise (Mizumura and Taguchi 2008). Acute muscle overuse in eccentric or supramaximal contraction, in repetitive contractions, or in sustained postural muscle overload, causes muscle damage, local release of neuropeptides, cytokines, and other inflammatory mediators that result in local edema, capillary compression, and energy depletion. Muscle sarcomere disorganization occurs with supramaximal and eccentric muscle contraction (Armstrong et al. 1983; Newham et al. 1983). Inflammatory marker elevation has not always been found after eccentric exercise, however. Muscle pain in vitamin D deficiency is also associated with type II muscle atrophy. Thus, it is likely that when type II muscle fibers are either injured or atrophied, and dysfunctional, the remaining type II muscle fibers are overloaded, or there is overloading of type I muscle fibers, which can lead to muscle pain through the release of chemical mediators such as neurotransmitters, ions such as protons or potassium, and cytokines, which can in turn result in the activation of peripheral nociceptors. There are no data as yet to directly link these findings to the development of the trigger point, even though these observations are suggestive and intriguing in that respect.

Muscle overload may result in DOMS (Graven-Nielsen and Arendt-Nielsen 2008), but pain and soreness in DOMS are not necessarily correlated with the structural changes described above. Changes in muscle induced by overuse share the some of the same characteristics as acute muscle injury, repetitive motion-induced pain, and chronic muscle pain (Ernberg 2008). There is no necessary association between postexercise muscle damage, inflammation, and pain (Dannecker 2008). DOMS is an imperfect model for MPS. Nevertheless, muscle breakdown caused by acute or chronic muscle overload resulting in local hypoxia and ischemia best fits the picture of MPS, largely based on the time course of pain and the biochemical changes in the trigger point milieu described by Shah et al. (2005).

2.9.2 Postural Stresses

Postural stresses are another form of mechanical muscle stress that has been considered to be a cause of MTrP formation and activation. Spondylosis with joint hypomobility results in a kind of postural dysfunction that is associated with neck, trunk, and low back pain. MTrPs are seen in these conditions, but there are few studies that specifically show such an association. The prevalence of MTrPs in the upper trapezius, SCM, and levator scapular muscles in midcervical spine hypomobility was examined in a pilot study by Fernandez-de-las-Peñas et al. (2006b), but the association of trigger point presence with hypomobility did not reach statistical significance. This study limited the trigger point evaluation to the region of the scapular insertion of the levator scapulae and to the vertical fibers of the trapezius muscle in the neck, in addition to the SCM. In fact, a previous study by the same investigator showed a statistically significant relationship between trigger points in the upper fibers of the trapezius muscle and C3/4 hypomobility (Fernandez-de-las-Peñas et al. 2005c).

2.10 Pain Initiation in Myofascial Pain Syndrome

2.10.1 Inflammatory Pain Models

Pain is central to the clinical presentation of MTrP syndromes. It is the major reason why patients seek care. The inflammatory model of muscle pain has been well studied. Carrageenan induces an increased activity of muscle nociceptors and dorsal horn neurons that results in central sensitization. Carrageenan-induced self-limited inflammatory hyperalgesia produces a state of chronic-latent hyperalgesia revealed by injection of prostaglandin E_2 10 days after the intramuscular injection of carrageenan, a state that lasts 14 days without attenuation (Dina et al. 2008). This is an important observation, because the clinical model of myofascial pain is often subacute or chronic, and recurrent. However, the relevance of this model to the development of painful MTrPs is not established, as no models of inflammatory-induced trigger points are known.

Theories that attempt to account for pain generation in MPSs must take into account the apparent lack of overt muscle injury. There have been few attempts to biopsy trigger points. It is difficult to localize a trigger point in a situation suitable for biopsy, and data are therefore scarce to nonexistent. However, absence of serum creatinine phosphokinase (CPK) elevation in MPS suggests that there is no component of inflammatory myositis in trigger point development. Information available to date suggests that ultrastructural muscle fiber derangement occurs, such as is seen in supramaximal and eccentric muscle contraction, and that significant pathophysiologic biochemical changes occur at the trigger point zone, including localized acidity (Shah et al. 2005).

2.10.2 Acid-Sensing Ion Channels

A model of nociceptive activation in muscle in the absence of muscle injury is the acid-sensing ion channel (ASIC). ASIC-3 is found in small sensory neurons that innervate muscle (51% of small muscle afferents), comparatively more than in sensory neurons that innervate skin (Molliver et al. 2005). One well-studied noninflammatory model of muscle pain consistent with trigger point-induced pain showed that long-lasting bilateral hyperalgesia is induced by two intramuscular injections of acidic (pH 4.0) saline given 5 days apart (Sluka et al. 2001). Muscle pH decreases to pH 6.0 for only 6 min in this model. No local inflammatory changes take place. A central response occurs in the spinal cord dorsal horn, mediated through NMDA and glutamate receptor activation, producing widespread hyperalgesia (Skyba et al. 2002). Phosphorylation of cAMP-responsive element-binding protein (CREB) is increased in the spinal cord in this model (Sluka 2002). Hyperalgesia is reversed by blockade of NMDA receptors, glutamate receptors, and the cAMP pathway. Furthermore, ASIC-3 knock-out mice do not develop central hyperalgesia when challenged with two acidic saline injections (Sluka et al. 2003). Additionally, acidic buffer injected into the anterior tibial muscle in humans produces mechanical hyperalgesia and referred pain (Frey Law et al. 2008b).

A further complexity in this system is related to nerve growth factor-related neurotrophins, including neurotrophin-3 (NT-3), that are expressed in muscle; most muscle afferents are responsive to NT-3. Mice that over-express NT-3 do not develop hyperalgesia when challenged with acidic saline intramuscular injections. NT-3 injected into muscle prior during development of hyperalgesia blocks the onset of hyperalgesia, but has no effect once hyperalgesia has occurred (Gandhi et al. 2004). Antagonists to ASIC suppress pain induced by carrageenan and eccentric exercise-induced muscle hyperalgesia (Fujii et al. 2008). ASIC-3 is necessary for the development of central hyperalgesia and chronic widespread pain, and NT-3 is seen as preventing central sensitization (DeSantanta and Sluka 2008). These findings are of great interest as a possible mechanism for trigger point pain generation in humans.

2.10.3 Serotonergic Mechanisms

There are other potential mechanisms for activation of peripheral nociceptive receptors that involve different chemical mediators and neurotransmitters such as glutamate, bradykinin, and potassium. Serotonin (5-HT) is one neurotransmitter that is elevated in the active trigger point milieu (Shah et al. 2005). 5-HT receptors are primarily pronociceptive (pain-promoting) in the periphery, acting directly on afferent nerves and indirectly by release of other mediators (e.g., substance P and glutamate). The 5-HT2A subtype, expressed in CGRP-synthesizing dorsal root

ganglion neurons, potentiates peripheral inflammatory pain (Okamoto et al. 2002). 5-HT has both antinociceptive and pronociceptive effects centrally. Centrally, 5-HT activates the descending pain-inhibitory system. It also activates the facilitatory responses that lead to central sensitization. 5-HT acts peripherally in masticatory afferent fibers from the trigeminal nerve. This activity is reduced by the 5-HT antagonist tropisetron (Sung et al. 2008). 5-HT antagonists block the algesic effect of 5-HT when injected into some, but not all, muscles (Christidis et al. 2005). Tropisetron and granisetron have produced mixed results when injected into muscle, but on balance give relief from MTrP pain. Local injection of 5-HT into muscle reduces pain in some models, further supporting the concept that 5-HT_3 receptor has a peripheral role in mediating pain (Ernberg 2008). These observations have theoretical implications for the generation of pain from trigger points, and they also have therapeutic implications, as targeting the actions of 5-HT peripherally and centrally may be effective in modulation of trigger point pain syndromes (Müller and Stratz 2004).

2.10.4 Calcitonin Gene-Related Peptide

CGRP is elevated in the trigger point milieu of active trigger points (Shah et al. 2005). CGRP is produced in the dorsal root ganglion. It is released from the peripheral terminals of primary sensory afferents, and centrally in the spinal cord dorsal horn. It is present in the nerve terminals of nociceptive afferent fibers. CGRP facilitates synaptic plasticity in the spinal dorsal horn (Bird et al. 2006). It enhances the central release of glutamate and aspartate, and increases neuronal responsiveness to excitatory amino acids (EAA) and to substance P in dorsal horn nociceptive neurons and in wide dynamic range neurons. Glutamate is an EAA that activates peripheral EAA receptors and excites and sensitizes muscle afferent fibers (Cairns et al. 2002). CGRP acts through second-messenger systems utilizing protein kinases A and C to initiate and maintain central sensitization (Sun et al. 2004). The peripheral release of CGRP contributes to the induction and maintenance of neuropathic pain (Jang et al. 2004).

2.10.5 Spinal Modulation of Pain

Descending facilitation and inhibition of ascending nociceptive impulses are important mechanisms of modulating pain perception. Tonic, noxious stimulation inducing muscular pain produced by injection of hypertonic saline, and cold pressor pain, suppress descending inhibitory pain controls in humans. However, modulation of the descending pain modulation system is complex, in some cases facilitating, rather than inhibiting, ascending nociceptive stimuli.

2.11 Epidemiology of Myofascial Pain

2.11.1 Prevalence Studies

Studies on the epidemiology of MPS are hampered by the lack of consensus about the criteria used to diagnosis the condition. This problem is addressed in the next section *Diagnosis of MPS*.

There are no prevalence studies of MPS per se in the general population. Latent trigger points were reported in about 11% of subjects in Thailand (Chaiamnuay et al. 1998). Musculoskeletal pain in general is estimated to have a prevalence rate of 20% in one Canadian study (Badley et al. 1995). Pain complaints were found in 32% of a university primary care general internal medicine practice series of 172 patients of which 30% were found to have myofascial pain (9% of the total number of patients) (Skootsky et al. 1989). One pain rehabilitation referral center reported that 85% of their patients were diagnosed with MPS (Fishbain et al. 1986). In a pain treatment referral program known for its interest in myofascial pain, within a larger neurological practice, 93% of persons with musculoskeletal pain had MTrPs (Gerwin 1995).

Most other studies of the prevalence of MPS have been confined to special populations. MPS was detected in 61% of a series of 41 complex regional pain syndrome subjects (Rashiq and Galer 1999). A study of 243 female sewing machine operators showed a MPS prevalence of 15.2% in neck and shoulder muscles compared to 9.0% among 357 control women (Kaergaard and Andersen 2000). Single mothers, smokers and those with perceived low support from colleagues and supervisors were at a higher risk of developing neck and shoulder pain.

2.11.2 Gender Differences

Sex-related differences are known in a variety of painful conditions, including migraine headache and fibromyalgia. Differential responses based on gender are known to occur in musculoskeletal pain (Treaster and Burr 2004; Ge et al. 2006). Days absent from work and expenditures for healthcare are greater for women than men (Rollman and Lautenbacher 2001). Occupational neck and shoulder pain is more common in women than in men (Bergenudd et al. 1988). Pressure pain thresholds (PPT) are also lower for women, signifying greater hypersensitivity to mechanical stimulation. Injection of hypertonic saline in bilateral trapezius muscles, to simulate the real-life bilateral shoulder pain commonly experienced in certain work situations, resulted in greater pain inhibition in men than women 7.5 and 15 min after injection (Ge et al. 2006). Baseline pain pressure threshold was lower in women, but the increase in PPT after a second injection of hypertonic saline was much greater in men than in women. The greater increase in PPT in men represents an increased hypoalgesia or increased nociceptive inhibition which is likely to be central. Differences in pain and electromyographic changes associated

with sustained trapezius muscle contractions show that pain-induced changes in motor control strategies differ in men and women. Sustained contraction of the trapezius muscle is more common than other sustained shoulder muscle activation in real-world activities. In this model, pain is induced by injection of hypertonic saline into the trapezius muscle. The root mean square (RMS) and mean power frequency (MPF) computed from electromyographic signals showed differences between men and women (Ge et al. 2005). The RMS slope increased and the MPF slope decreased (less negative) with muscle pain in men but not in women. Glutamate-evoked muscle pain is also greater in women, whereas hypertonic saline-evoked pain is not, and glutamate-evoked afferent discharges are greater in female rats than in males, suggesting that the effect is mediated peripherally (Cairns et al. 2002; Arendt-Nielsen et al. 2008a, b). One explanation is that there is an increased central sensitization in women, but an alternative explanation is that descending inhibition is weaker in females than in males.

The exact mechanism(s) of gender differences to muscle pain remain(s) to be identified. However, certain effects of sex hormones on pain mechanisms are known. Estradiol modulates NMDA receptor activity in the spinal dorsal horn, increasing the nociceptive response to colorectal distension in rats (Tang et al. 2008). Estradiol also modulates the excitability of primary sensory afferent nerves (Hucho et al. 2006). A role for estrogen in the development of hypersensitization has been considered (Isselee et al. 2002). In contrast, one study of sex differences in recalled and experimentally induced muscle pain showed no difference between male and female subjects (Dannecker et al. 2008).

2.11.3 Hypermobility

Hypermobility or ligamentous laxity seems to be a relevant risk factor for the development of MPSs (Beighton et al. 1973; Gedalia et al. 1993; Hudson et al. 1995; Sacheti et al. 1997; Ferrell et al. 2004; Adib et al. 2005; Nijs 2005; Ofluoglu et al. 2006). The mechanism is thought to be the more constant contraction of muscle needed for joint stability that the ligaments are unable to provide. Those persons with recurrent large joint dislocations or subluxation seem to be at an even higher risk of developing trigger points.

2.12 Diagnosis of Myofascial Pain Syndrome

2.12.1 Reliability of Manual Identification of Trigger Points

The reliability of MTrP diagnosis has long been a debatable point in the medical literature, because there had been no laboratory or imaging technique that was capable of confirming the clinical diagnosis. Diagnosis had been possible only by

clinical history and examination, very similar to migraine and tension-type headache. Nevertheless, the literature was critical of the ability to make a diagnosis of MTrP pain until quite recently. Part of the problem was undoubtedly the failure to understand the nature of referred pain, an issue put to rest with the advances in the understanding of pain neurophysiology. Several attempts to demonstrate the clinical efficacy of manual physical examination prior to 1997 failed. It was only in 1997 that the first paper to establish interrater reliability in trigger point identification was published (Gerwin et al. 1997). The most reliable findings in that study were localized tenderness, presence of a taut band, and pain recognition. The four examiners in that study, all with some experience in the examination of trigger points, failed to achieve significant agreement on a first trial because (1) too many muscles were included in the evaluation for the time allotted (20 muscles in 15 min), (2) not all examiners could identify all muscle selected on the first trial, and (3) not all examiners agreed on the physical findings of the features they were evaluating, particularly the taut band and the twitch response. A 3 h training period was undertaken to ensure that all examiners were examining the same muscles, and that the examiners agreed on the nature of the findings they were evaluating. The examination of five muscles bilaterally, or ten muscles per subject, was conducted with the examiners blinded as to whether the subject had myofascial pain or was a normal control, and blinded to each other's findings. Interrater reliability was then quite good for all features evaluated. The best agreement was for the features taut band, tenderness, and pain recognition. These features became the recommended features necessary for identifying a trigger point. That study also showed that not all muscles are equally easy to examine, and not all features of the trigger point, such as the local twitch response, are equally easy to identify (Fig. 2.14).

The efficacy of physical examination in detecting MTrPs has been confirmed by subsequent studies. Interrater reliability has been demonstrated to a precision of a square centimeter or so within a single muscle (Sciotti et al. 2001), indicating that examiners could independently identify the same taut band region. Interrater reliability of MTrP palpation in shoulder muscles was successfully shown by Bron et al. (2007). Referred pain and the "jump sign" had the greatest degree of agreement among the blinded examiners. Identification of a nodule in a taut band and eliciting a twitch response had the two lowest degrees of agreement. Recognition of usual pain was not evaluated in that study. Degree of agreement among examiners varied with the muscle studied, and even within different areas of a single muscle. The Kappa Coefficient for agreement for identifying a palpable nodule within a taut band varied from 0.11 to 0.75 (percentage of agreement varying from 45% to 90%) in the Bron et al. study. In clinical practice, feedback from patients allows assessment of reproducing clinically relevant pain elicited by palpation. Studies relating the presence of trigger points to treatment outcome (find a trigger point, inactivate the trigger point, measure outcome) have not been done. Such a study would help to establish the essential features of the trigger point needed to treat effectively.

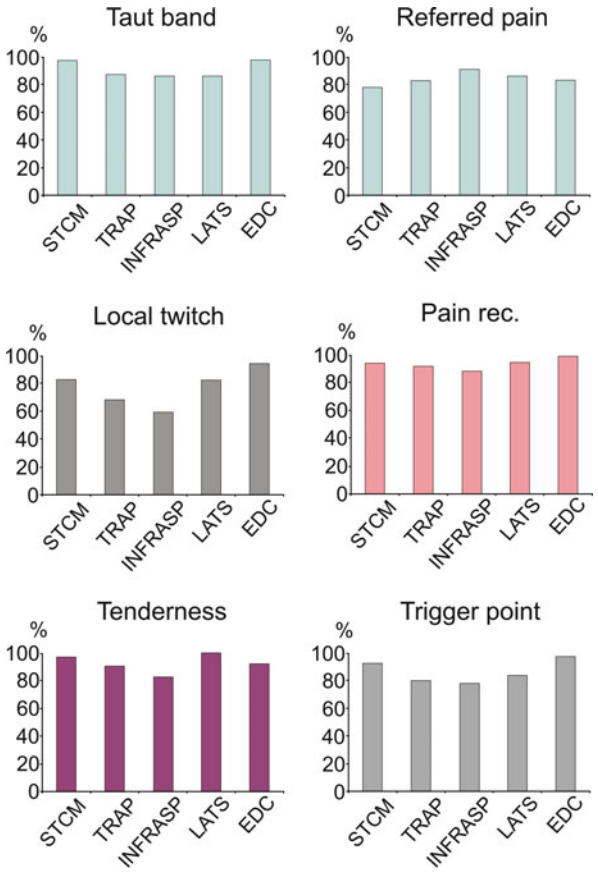


Fig. 2.14 Interrater reliability was high among four blinded examiners evaluating trigger point-related phenomena and making a global assessment of the presence or absence of trigger points in specific muscles. The charts provide data on percent of agreement, but the kappa coefficient of agreement was also very high. There is nevertheless variation among the different factors and among the different muscles, indicating that some features are more difficult than others to identify, and that all muscles are not as easy to examine. *STCM*, sternocleidoid muscle; *LATS*, latissimus dorsi muscle; *EDC*, extensor digitorum communis muscle. Gerwin et al. (1997)

2.12.2 Consensus Studies and Systematic Reviews

A review of the criteria used to diagnose MTrPs concluded that there was limited consensus on case definition of MTrP syndrome (Tough et al. 2007). Specifically, the authors note that there has not been a consensus on the criteria for the definition of MTrP syndrome, despite the majority of authors citing Simons et al. (1999) as the authoritative source for such criteria. For example, of 57 papers citing Simons et al. (1999) as the source for the criteria defining MPS, the authors found that only 12 papers used the criteria correctly. The authors also noted that 30 papers that used

algometry cited Fischer (1988, 1997) as the authority for defining MTrPS criteria, but that only one applied the criteria as described by Fischer. Over half of the studies used two criteria: (1) tender spot in a taut band of skeletal muscle, and (2) recognition of usual pain or predicted pain referral pattern. The authors suggested that claims for effective interventions in treating MTrP syndrome should be viewed with caution until there are better-validated criteria for case definition. Myburgh et al. (2008) also concluded that the methodological quality of the majority of studies for the purpose of establishing trigger point reproducibility was poor.

Another systematic review of trigger point identification studies concluded that no study reported the reliability of trigger point diagnosis using what they considered to be currently proposed criteria for symptomatic patients (Lucas et al. 2009). The authors state that "authorities" describe a trigger point as "a hyperirritable nodule located within a taut band of skeletal muscle that when palpated is tender and produces referred pain." The authorities listed are the authors of the major text on myofascial pain (Simons et al. 1999). The other references are again to David Simons, except for one reference to Tough (cited above). In fact, the hyperirritable "nodule" does not have to be a palpable nodule at all. However, as pointed out in this chapter, the taut band is a constant finding in active and latent trigger points, and is the only objective finding on physical examination. It is true, however, that no study has looked at the minimum requirements for the diagnosis of MTrPs in light of what is needed to treat them effectively by trigger point inactivation. Dommerholt and Gerwin found that identification of a taut band, tenderness of the taut band, and reproduction of the patient's pain were sufficient to guide effective treatment (Gerwin and Dommerholt 2001, unpublished data).

The development of criteria for the diagnosis of MPS was the object of an attempt initiated at the 1998 International Myopain Congress in Italy. A multicenter study was developed, but in the end only two centers completed the study. In both of theses conditions, central sensitization, and to some extent peripheral sensitization, play an important role in pain symptomatology. The overlap between these tow conditions may be considerable, and both have to be addressed. A merged data evaluation of the 80 subjects in the study showed that local tenderness, referred pain, and a palpable taut band were useful. However, agreement on diagnosis for both centers was weak (Kappa = 0.32; Staffel et al. 2007).

2.12.3 Objective Criteria

There has been no attempt to validate the clinical criteria with any objective criteria such as electromyographic evidence of endplate noise (Simons et al. 2002) or the biochemical changes identified with active MTrPs as reported by Shah et al. (2005). Skin resistance has been evaluated as a means of distinguishing MTrPs in a superficial muscle from normal muscle tissue. Trigger points, whether active or latent, cause decreased skin resistance that can be used for identification, at least in a superficial muscle (Shultz et al. 2007).

Magnetic resonance elastography may emerge as an effective tool for identifying the trigger point taut band. The technique involves the introduction of cyclic waves into the muscle, and then using phase contrast imaging to identify tissue distortions. The speed of the waves is determined from the images. Shear waves travel more rapidly in stiffer tissues. The harder taut band can thus be distinguished from the surrounding normal muscle (Fig. 2.15; Chen et al. 2007, 2008).

2.12.4 Pain from Bone and Tendon

Another diagnostic issue has to do with the relative responsiveness of musculoskeletal tissues. Pain can arise from the junction of bone and tendon, from tendon alone,

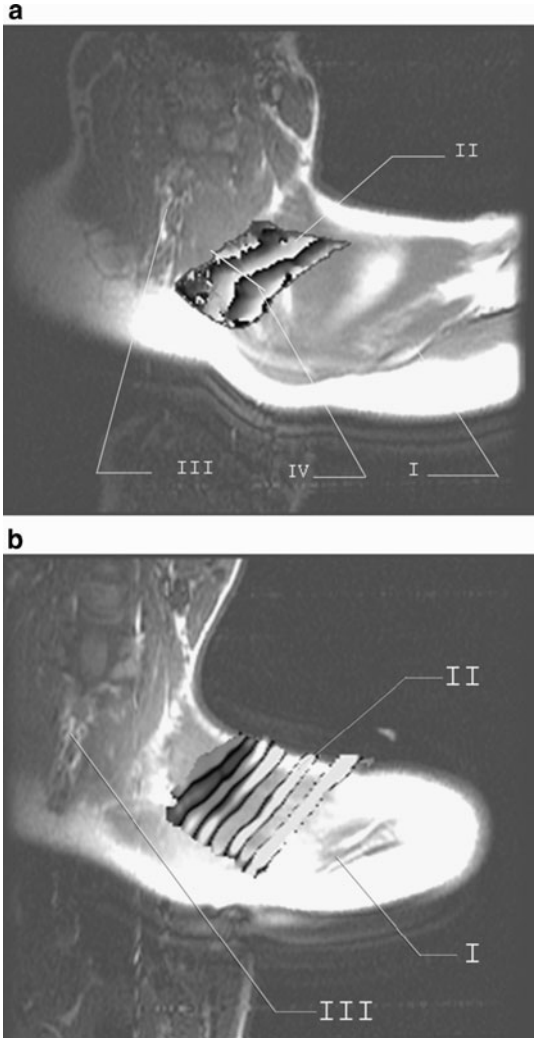


Fig. 2.15 The taut band can be visualized by high resolution ultrasonography and its effect can be seen with magnetic resonance elastography, as shown in this figure of the trapezius muscle. (**a**) Shows the chevron deformity caused by more rapid transmission of a shear wave induced by an oscillating sensitizer, in the stiffer taut band, than in normal control (**b**). Thus, the taut band or its effect can be objectively demonstrated. Clin Biomech 23:623–629. **a** (*I*) scapular spine, (*II*) chevron-shaped wave fronts observed in the region of the palpated taut band, (*III*) cervical spine, (*IV*) the *white line* represents the location of the taut band. **b** (*I*) scapular spine, (*II*) planar waves in the upper trapezius, (III) cervical spine. Chen et al. (2008), used with permission

and from muscle, or from a combination of any of these components. Hypertonic saline and mechanical stimulation at all three sites showed greater pain to injection of the proximal bone–tendon junction and tendon than muscle referred pain predominantly from tendon and bone–tendon junction stimulation, indicating that proximal bone–tendon junction and tendon are more sensitive and susceptible to sensitization by hypertonic saline (Gibson et al. 2006). This study suggests that pain from tendon and bone–tendon junctions must be considered among the sources of musculoskeletal pain, as well as muscle.

2.13 Differential Diagnosis

2.13.1 Differential Diagnostic Considerations

The diagnosis of MPS with trigger point tenderness and referred pain is enough to initiate treatment at a symptomatic level. However, the diagnosis of MPS is only the beginning of the diagnostic and treatment process. Additional steps are necessary to fully address a patient's pain problem. Trigger point-induced pain must be related to the patient's complaint. Many people have active or latent trigger points that are not related to their clinical problem, or are irrelevant or confounding comorbidities. A striking example is a woman complaining of neck pain and suboccipital headache who had trigger points in the posterior cervical and suboccipital muscles. Treatment of the trigger points relieved her headache for a day, but the headache recurred. She had cerebellar metastases that caused her headache. Thus, as this woman illustrates, trigger points may contribute to a clinical syndrome, but may not be the only relevant or primary aspect of the problem.

2.13.2 Trigger Point-Initiating Factors

Trigger points do not arise de novo, without cause. Trigger points are always caused by something. The initiating factor may be evident, but this is not always the case. Dr. Janet Travell liked to call the hidden nature of the cause of pain the "Mysteries of the History" (Travell 1990), indicating that a thorough history was a most useful diagnostic tool in identifying the often enigmatic nature of the underlying cause of myofascial pain. The list of conditions that must be considered reads like a textbook classification of diseases, encompassing endocrine disorders, connective tissue diseases, genetic deficiency states, infectious diseases, and cancer among others. The conditions discussed in the section on perpetuating factors in this chapter constitute an important body of underlying conditions to consider when dealing with myofascial pain but are not the only conditions to be considered.

2.13.3 Fibromyalgia

Fibromyalgia is an important differential consideration, because both conditions present as muscle pain, and because MTrPs can be found in patients with fibromyalgia. The question of whether fibromyalgia patients actually have trigger point pain is unsettled, although a preliminary study (Gerwin 1995) showed that 75% of patients who met the criteria for fibromyalgia had MTrPs. It is generally accepted that the two conditions are different. Myofascial pain has been described as a regional pain syndrome, although it may occur as a generalized muscle pain syndrome in up to 35% of patients (Gerwin 1995). The distinction between regional and generalized or widespread pain has been used to distinguish MPS from fibromyalgia, but that distinction is not valid because MTrP pain can be chronic and generalized and widespread, fulfilling the major diagnostic criteria for fibromyalgia. Moreover, persons with localized pain usually have pain in more than one region, and, in fact, have pain is several regions. Localized pain is relatively rare in clinical practice (Kamakeri et al. 2008).

2.13.4 Other Disorders to Consider

MPS should be differentiated from other causes of regional or generalized muscle pain syndromes that have specific causes, such as polymyalgia rheumatica, although such conditions can coexist with MPS as comorbid conditions. Such comorbid conditions can also be precipitating or perpetuating factors that initiate a MTrP syndrome or maintain it. An example of such a comorbid condition is vitamin D deficiency, which is known to be associated with musculoskeletal pain and with weakness. Connective tissue disorders such as rheumatoid arthritis certainly can have complicating, symptomatic myofascial pain. Localized and generalized osteoarthritis are important causes of MPS. MTrP pain in the shoulder region and in the hip muscles may be the presenting features of degenerative shoulder or hip joint pain. Iatrogenic causes of pain vary from dose-related drug-induced myopathy with statin-type drugs such as simvastatin and atorvastatin to postsurgical pectoralis major and latissimus dorsi trigger points following chest surgery.

2.13.5 Viscerosomatic Disorders

Visceral disorders such as heart disease, kidney stones, irritable bladder (Doggweiler-Wiygul and Wiygul 2002), irritable bowel syndrome, and endometriosis can all produce trigger point pain in body wall regions of referred pain. These may appear like primary MPSs when they are in fact secondary pain syndromes, representing viscero-somatic pain syndromes (Giamberardino et al. 2002).

2.13.6 Other Causes of Referred Pain

The referred pain patterns that are seen with MTrPs are not unique to trigger points. They are potentially seen in any painful condition associated with central hypersensitization. The segmental nature of the referred pain patterns means that there will be overlap in the regions of referred pain from different structures that have the same innervation. This is seen in cervical structures where MTrPs and zygapophysial joints with the same cervical root innervation have overlapping pain referral patterns. In clinical practice, this means that all structures that can generate local and referred pain in persons with WAD must be considered in making a diagnosis of the nature of the pain (Mense et al. 2003).

2.13.7 Mechanical Dysfunction

Hypermobility and structural bodily asymmetries such as leg-length inequality are mechanical causes of MPSs. Persons with chronic myofascial pain must certainly be assessed for these conditions. Those persons with hypermobility need to be further assessed for Chiari malformation and other related problems such as aortic aneurysms. Those persons who are iron-deficient need to be evaluated for the cause of iron deficiency, which may vary from menstrual blood loss to gastrointestinal blood loss, to inadequate iron in the diet, and to malabsorption from celiac disease. Consequently, there is both a need to treat the apparent presenting problem of myofascial pain and to investigate the underlying causes that led to trigger points and muscle pain.

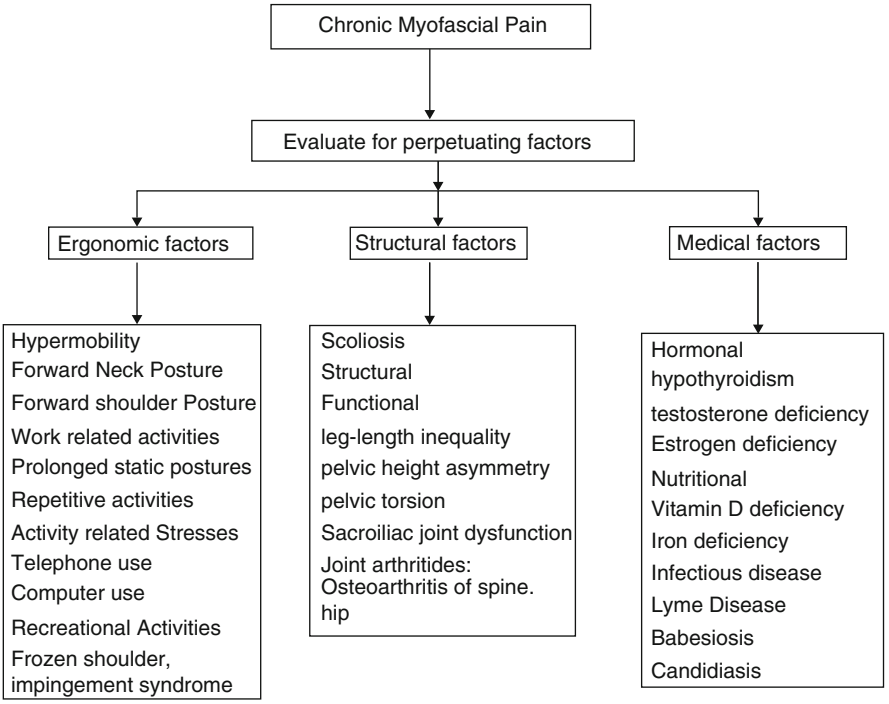
Thus, evaluation of a person complaining of musculoskeletal pain that is likely to include significant MPS begins with a thorough history of the nature of the complaint, the duration of the pain, the distribution of the pain, particular events surrounding the onset of the pain, and any co-incident injuries or illness at the time of onset. Particular aspects of the review of systems to be investigated include a sense of coldness (representing disorders of thermogenesis), fatigue, joint pains, and sleep disorders, and a menstrual history in women. Medications and supplements taken by the patient should be reviewed. The physical examination should include a general examination that includes an evaluation for hypermobility syndrome, scoliosis, pelvic movement asymmetries, joint hypomobility, and temporomandibular joint dysfunction, in addition to examination of muscle itself. Pertinent considerations for differential diagnosis are listed in Table 2.2.

2.14 Treatment

2.14.1 Treatment Principles

Treatment of trigger point pain syndromes is accomplished by inactivating the MTrP and then restoring normal body biomechanics to the extent possible.

Table 2.2 Evaluation of perpetuation factors



Treatment of the trigger point can help to establish the role of the trigger point in producing a patient's particular pain syndrome, can quickly reduce an acute pain, and can be an integral part of a physical therapy rehabilitation program. Those factors that initiated and maintained the pain need to be identified and corrected in order to sustain the gains made in the therapeutic treatment program. There are unanswered questions associated with each of these stages of treatment. Trigger point inactivation can be accomplished by either noninvasive means or by invasive means (needling or injecting the trigger point). Prophylaxis or prevention of trigger point recurrence can also be accomplished by invasive and by noninvasive means.

2.14.2 Manual Inactivation of Trigger Points

Manual inactivation of trigger points includes trigger point compression, spray and stretch, strain/counterstrain, ultrasound, and various forms of muscle stretching. There are few randomized, controlled studies of the effectiveness of manual therapy in trigger point inactivation (Fernandez-de-las-Peñas et al. 2005a). A limiting factor in assessing manual treatment techniques is the lack of uniform outcome measures. Most studies, but not all, used PPT or an 11-point Likert numerical or visual pain scale. However, some studies used the McGill Short-Form Pain Questionnaire or

Quality of Life assessments. Range of motion has also been used as an outcome measurement of effectiveness of treatment. Moreover, some trials evaluate just one manual therapy, and others have evaluated a combination of manual therapies. The conclusion of de las Peñas et al. (2005a) was that there was no rigorous evidence that the manual techniques studied have better outcome beyond placebo. The role of manual therapies was neither supported nor refuted by the results of their study. Rickard (2006) looked at some manual interventions, but only two of the studies included in the review used typical manual treatments of trigger points used by trained physical therapists (ischemic compression). These two studies demonstrated short-term (immediate) benefit, but had no long-term follow-up. One of the two studies looked at a combination of heat, range of motion exercises, inferential current, and myofascial release. The other study looked at ischemic compression.

The mechanism of pain reduction and softening of the taut pain by manual therapy remains speculative. Efficacy studies of a commonly used manual technique of trigger point inactivation, trigger point compression, have been infrequently carried out. A novel approach to evaluating the effectiveness of this approach utilized a digital algometer, demonstrating a benefit of manual compression with pain reduction and an increase in pain pressure threshold (Fryer and Hodgson 2005).

Massage has been used to treat muscle pain, if not MTrPs specifically. It has long been used, but little scientific evidence exists to support its use (Furlan et al. 2002). Deep tissue massage reduced mechanical hyperalgesia (lowered pain pressure thresholds) and decreased stretch pain in experimentally induced delayed onset muscle pain, whereas superficial touch only decreased stretch pain compared to the rest-only control group (Frey Law et al. 2008a).

In summary, data are either inadequate or conflicting regarding most manual therapies for the treatment of MPS (level **U**) (see Table 2.3 for the classification of levels of evidence).

Table 2.3 Levels of evidence

	Classification scheme		Classification of recommendations
Class I	1. Randomized, controlled trial 2. Objective outcome 3. Representative population 4. Equivalent baseline characteristics	A	Established as effective, ineffective, or harmful, requiring at least two consistent class I studies
Class II	1. Randomized, controlled trial 2. Lacks one of class I criteria	B	Probably effective, ineffective or harmful, requires at least one class I study or two consistent class II studies
Class III	1. Other controlled trials 2. Representative population 3. Outcome independently assessed or objective outcome measures	C	Possibly effective, ineffective, or harmful, requires at least one class II study or two consistent class III studies
Class IV	Studies not meeting Class I, II, or III criteria	U	Data inadequate or conflicting; given current knowledge, treatment or procedure is unproven

(Adapted from Editor's note to authors and readers 2009)

2.14.3 Noninvasive, Non-Manual Treatment Techniques

Treatments in this category include all forms of electrical stimulation, ultrasound, laser, and magnet therapies. One systematic review of the literature (Rickards 2006) reported that there is evidence to support the immediate benefit of transcutaneous electrical stimulation (TENS), but there are insufficient data to address long-term benefit. Preliminary evidence supported the use of magnetic therapy, but data were very limited and studies were of only moderate quality. The author found that conventional ultrasound was not more effective than placebo in neck and upper back pain based on the limited data available (one high-quality and two lower-quality studies). Ultrasound did not improve outcome when combined with massage and exercise (class I study) (Gam et al. 1998). One recent study, nonblinded, showed a short-term improvement in PPT with ultrasound (class IV study) (Srbely and Dickey 2007). A follow-up study by the same group showed reduction in pain following ultrasound treatment within muscles in the same nerve innervation segment (class I study) (Srbely et al. 2008). PPT values increased (less tenderness) in the infraspinatus muscle when trigger points in the supraspinatus muscle were treated, whereas there was no significant change in the PPT of the ipsilateral gluteus medius muscle, the control muscle, in this randomized, blinded, controlled study. Ultrasound treatment is probably effective in the treatment of trigger points (class B recommendation).

Another noninvasive approach to the inactivation of MTrPs that has created much interest is the use of low-level laser. There have been mixed results in the studies that have been randomized, controlled, and blinded. Earlier studies (class 1 studies) have shown benefit (Ilbuldu et al. 2004; Gur et al. 2004), but a more recent study showed no benefit (class I study) (Dundar et al. 2007). Low-level laser has level B recommendation of probably effective in the treatment of MTrP pain.

Thus, the data supporting recommendations regarding most noninvasive, nonmanual treatments of trigger points are either inadequate or conflicting (level **U**). Further studies are needed in order to base a treatment recommendation on medical evidence.

2.14.4 Invasive Treatment of Myofascial Trigger Points

Invasive treatment of MTrPs is generally done either by dry needling or by injection of substances. Deep dry needling was considered to be effective in some studies (Dommerholt et al. 2006b). It is a technique well tolerated, widely used, and deserves to be evaluated as a treatment of myofascial pain (Fig. 2.16). Dry needling of primary trigger points results in improved ROM and less tenderness at the primary trigger point site and at the site of satellite trigger points in its area of referred pain (Hsieh et al. 2007). Trigger point injection (TPI) is injection of some form of injectate through a needle inserted into the trigger point. The most common material injected is lidocaine. Lidocaine diluted to 0.25% was the most effective concentration associated with the least postinjection soreness (Iwama et al. 2001). Other substances than lidocaine have been used for injection, most commonly some

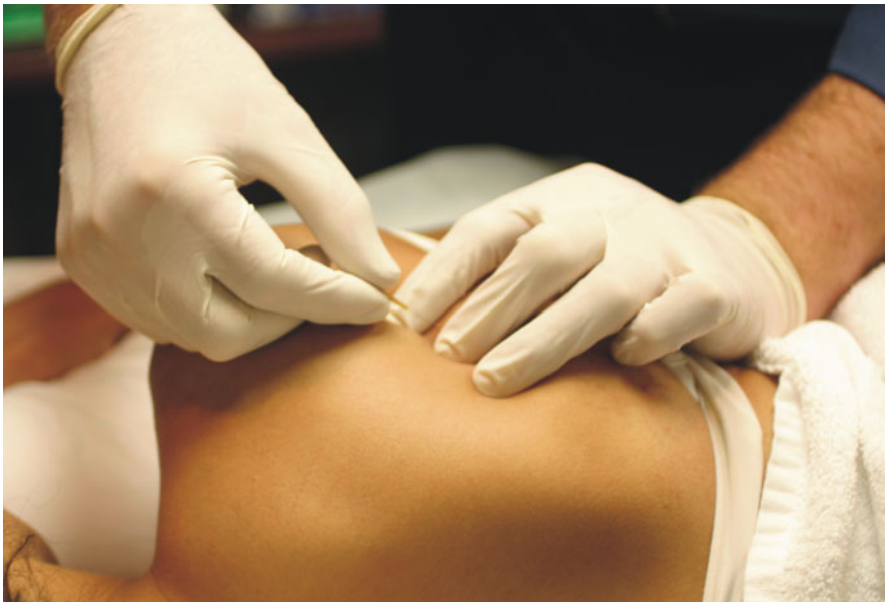


Fig. 2.16 Dry needling the right infraspinatus muscle as a way of inactivating a trigger point. Gloves are worn in keeping with the recommendations for universal precautions. The skin is cleansed. Landmarks are noted to clarify potential areas of danger and to clearly define the muscle to be treated. The trigger point is identified, and the taut band is palpated to identify the most tender region of the taut band. The taut band is fixed with the fingers, and then the dry needling begins. Multiple insertions are performed in order to elicit a local twitch response. The muscle is lengthened afterward, and moist heat is applied

form of corticosteroid. Cummings and White (2001) reviewed 23 papers, and found the effect of needling was independent of the material injected. They found no trials of sufficient quality or design to test the efficacy of any needling technique over placebo (level **U**). Their conclusion was that direct needling of trigger points appears effective, that in three trials there was no difference between dry needling and injection, and that controlled trials are needed to determine if TPIs are more effective than placebo. An updated review found 15 randomized, controlled studies that met their inclusion criteria (Scott et al. 2009). However, small sample sizes, deficiencies in reporting, and heterogeneity of the studies precluded a definitive synthesis of the data. TPI appeared to relieve symptoms when it was the sole treatment for whiplash syndrome, and for chronic neck, shoulder, and back pain. The authors concluded that there is no clear evidence that TPI is ineffective or beneficial, but that it is a safe procedure in experienced hands (level **U**). There is no evidence to support or negate the use of any injectate over dry needling.

One study compared TPI with lidocaine with intramuscular stimulation using acupuncture needles (dry needling; Ga et al. 2007a). This study is consistent with current clinical practice, as dry needling currently is most commonly done with acupuncture needles. The study demonstrated the effectiveness of both techniques

in providing pain relief, better relief of depression with dry needling (!), and improvement in passive range of motion with both treatments. Post-treatment soreness was the same in both groups. Local twitch responses were elicited in 97.7% of subjects treated, an indication that the needle placement was in the trigger point zone. An additional study by the same group evaluated peripheral dry needling with and without the addition of dry needling of the multifidi muscles (paraspinal dry needling) in the neck (Ga et al. 2007b). Although the addition of needling multifidi gave a small statistical advantage, both techniques were effective in relieving pain at 1 month (class III studies). There is, however, a major difficulty in finding appropriate placebo or sham treatments in controlled studies. Many placebo treatments of MTrPs are active, not inactive placebos. Attempts to enhance the needle effect on trigger points include electrical stimulation through needles inserted into the myofascial trigger zone (needle electrical intramuscular stimulation or NEIMS). Visual analog scale rating of pain, PPT, and range of motion improved among subjects treated with NEIMS (class III study) (Lee et al. 2008). The conclusion is that dry needling and acupuncture are each possibly effective based on available studies (level C recommendation). However, much depends on the outcome measures and the goal of treatment. In clinical practice an immediate reduction in trigger point pain and an improvement in ROM are usually seen with trigger point needling (Nazareno et al. 2005). The benefit lasts from days to a week or 10 days.

Acupuncture trigger point needling is a term used to describe inserting the acupuncture needle into a muscle trigger point. It has been used to treat MTrPs in a manner identical to the dry needling technique described by physical therapists, physicians, and others. It has been shown to be effective in treating chronic neck pain and chronic low back pain (Itoh et al. 2004, 2006a, b). Blinding using sham needles was effective in these two studies (class I studies). Acupuncture was more effective than dry needling and both were more effective than sham acupuncture in reducing MTrP pain (VAS) and ROM (Irnich et al. 2002). These studies further support the effectiveness of acupuncture and dry needling in treating MPSs. However, another systematic review of acupuncture and dry needling (deep needling techniques) concluded that there was only limited evidence from one study showing that deep dry needling was beneficial compared with standardized care (Tough et al. 2008). Some studies were criticized because trigger points were not convincingly the sole cause of pain, although in clinical practice that is often the case. Treatment techniques (depth of insertion of the needle, location of needle placement, duration of needle insertion) varied, and cotreatment varied, all of which reduced the comparability of studies.

A central modulating effect occurs with dry needling of MTrPs. Dry needling of key trigger points diminishes satellite trigger point activity (Hsieh et al. 2007). In this single-blinded, randomized, controlled trial, inactivation of infraspinatus trigger points had a beneficial effect on trigger point manifestations (pain intensity and PPT) in ipsilateral proximal and distal upper extremity muscles (class I study).

The mechanism of action of trigger point needling has never been adequately elucidated. The results of dry needling seem to be about as effective as injection of local anesthetic, suggesting that local anesthetic is not absolutely necessary. Thus,

it seems that it is the mechanical action of the needle itself that inactivates the trigger point. Some consideration has been given to disruption of the muscle cell wall by the needle, causing alterations of calcium influx into the cytoplasm. This mechanism does not seem credible, as disruption of the cell wall on a macroscopic basis would be likely to result in major cell function disruption. Well-documented trigger point inactivation associated with the injection of bupivicaine was significantly reversed with intravenous naloxone (10 mg) (Fine et al. 1988). This strongly suggests that endogenous opioids are involved in the needle-induced relief of pain and in the reversal of the physical manifestations of the trigger point. There has been no follow-up to this study. Furthermore, there have been no studies of the effect of naloxone on the manual inactivation of the trigger point.

2.14.5 Botulinum Toxin

Botulinum toxin has been used to inactivate trigger points. Theoretically, botulinum toxin should act like a long-lasting TPI if it acts to prevent the development of the trigger point or inactivates it. One study showed that it reduced or blocked endplate noise at the trigger zone in the rabbit (Kuan et al. 2002). A number of randomized, controlled, double-blind studies have been conducted, but many were small studies or did not utilize appropriate criteria for identification of trigger points. In addition, the variable amounts of toxin used in the studies, the lack of documentation of injecting precisely at the trigger zone, and lack of attention to treat the entire relevant functional muscle unit may all have contributed to the inability to show efficacy (Ho and Tan 2007). Injection of up to 50 units of botulinum toxin in up to five active trigger points in the neck and shoulders failed to reduce pain more than the placebo control group (Ferrante et al. 2005). Both groups received myofascial release physical therapy, amitriptyline, ibuprofen, and propoxyphene napsylate/APAP, which may have influenced the outcome in this 12-week study. There are some new, interesting substances used for TPI that are presently being explored, such as bee venom and tropisetron (Stratz and Müller 2004; Müller et al. 2006). Tropisetron is a 5-HT3 antagonist that has been shown to alleviate pain in MTrP pain syndromes. It also has a more widespread analgesic effect. It may be the first specific injectate shown to have a positive benefit in the treatment of MTrP pain syndromes.

Baldry's technique of superficial dry needling has never been subjected to adequate study (Baldry 2002). The needle is inserted into the subdermal layers of skin over the point of tenderness. Baldry proposes that this technique is effective and less invasive than inserting needles into muscle, and avoids the potential complications of pneumothorax and other complications of deep needling.

Trigger point dry needling and TPI, as presently performed: (1) provide immediate relief of pain, (2) are useful diagnostically to see if a particular pain syndrome is myofascial in nature, and (3) are most effective when used to facilitate physical therapy. As the systematic reviews show, there is a need for further studies examining these outcomes.

2.15 Perpetuating Factors

2.15.1 Introduction to Perpetuating Factors

Patients with chronic myofascial pain often have problems that predispose them to developing MPS. These factors need to be identified, and treated where appropriate and possible. An illustrative example is a young woman with the complaint of headache, fatigue and widespread pain, a common constellation of complaints. More detailed history elucidated the complaint of a sense of chronic coldness, restless legs at night, a very restless sleep, and heavy menstrual periods. Her laboratory tests showed her to be iron-deficient. Iron deficiency contributes to or causes restless leg syndrome (RLS) that in turn can produce nonrestorative sleep, contributing to fatigue. Iron deficiency also contributes to impaired thermogenesis, producing a sense of coldness. Both poor sleep and iron deficiency can lead to muscle achiness and trigger point development. This patient was treated with iron replacement and sent to her gynecologist to control her menorrhagia. No other treatment was undertaken. She improved satisfactorily with iron supplementation.

2.15.2 Iron Insufficiency

Iron deficiency is a common condition in women with muscle pain. Iron is essential for the generation of energy through the cytochrome oxidase system. The clinical complaints of feeling cold "through and through," (rather than simply cold hands and feet), reduced exercise endurance, and generalized pain are indicators that iron insufficiency may be a factor in a person's myofascial pain. The relationship between low or insufficient iron stores and MTrPs has never been clearly established in clinical studies. However, improvement in endurance, lessening of an abnormal sense of coldness, and a decrease in muscle pain, seen when iron insufficiency is treated with iron supplementation in women with MPS, are suggestive of such a connection.

Iron stores are best assessed by measuring serum ferritin levels. Anemia is associated with ferritin levels of $\leq$10 ng/ml. However, serum levels of 15 ng/ml are associated with depletion of freely mobilizable iron stores in muscle, liver, and bone marrow, the first stage of iron deficiency. The second stage of iron deficiency is microcytosis. The third stage of iron deficiency is anemia, by which time iron bone marrow stores are undetectable. Thus, microcytic, hypochromic anemia is an inadequate indicator of iron deficiency in persons with myalgias because it misses the clinically important early stages of iron deficiency. Symptoms such as muscle achiness, chronic tiredness, unusual fatigue with exercise, and a sense of coldness begin with the first stage of iron deficiency.

Iron deficiency in muscle occurs when muscle ferritin is depleted. This occurs at serum ferritin levels of about 15 ng/ml. Iron deficiency has been defined as a level

of iron associated with anemia. Iron deficiency can cause poor endurance, impaired thermal regulation, fatigue, and muscle pain. Iron levels vary with age and sex. Iron levels are low in adolescence, falling with increased growth, and with the onset of menstrual blood loss in girls and young women. Iron levels rise again in adulthood and when women become postmenopausal. This variability is important when assessing iron stores in persons with muscle pain, particularly adolescent girls and premenopausal women. The prevalence of iron deficiency in females age 12–49 is 9–16%, but is higher in African–Americans and Hispanics (19–22%; Seaverson et al. 2007). Iron insufficiency is most often seen in women because of menstrual blood loss. It is seen in men primarily in instances of gastrointestinal blood loss due to ingestion of nonsteroidal anti-inflammatory drugs (NSAID) or from bowel cancer. It may also be seen in vegans, and in persons with iron-poor, aberrant dietary habits.

Simons' Integrated Hypothesis of the Trigger Point (Simons et al. 1999) proposes that MTrPs develop as a result of an energy crisis within muscle. A deficiency of freely accessible iron in muscle creates an energy crisis by limiting cytochrome oxidase energy-producing reactions. An iron–sulfur protein functions in the cytochrome b–c_1 segment in electron transfer reactions of the mitochondrial respiratory chain (Edwards et al. 1982), and a ferrous–oxy heme intermediate is also present in the cytochrome oxidase system (Verkhouvsky et al. 1996). In addition to iron-deficiency states, cytochrome oxidase reactions can be blocked when nitric oxide binds to ferrous heme iron (Cooper 1999). Both norepinephrine and energy metabolism are altered in iron-deficient rats (Brigham and Beard 1995). Iron is thus essential for the functioning of the cytochrome oxidase energy-producing system.

Optimum ferritin levels are unknown for normal muscle function. However, RLS, a condition that can be caused by iron deficiency, is associated with serum ferritin levels below 50 ng/ml (Wang et al. 2009). Serum ferritin was lower than 20 ng/ml in 50% of adolescents and children with RLS, and below 50 ng/ml in 83% of cases. These figures cannot be extrapolated to myalgia, but suggest a range of optimal values for good health in general. For further guidance, the upper limit of normal in premenopausal women is 150 ng/ml, whereas in postmenopausal women and men it is 300 ng/ml. RLS produces sleep deprivation which in turn is associated with muscle pain (Moldofsky 2008). Thus, there is a direct and an indirect effect of iron deficiency on muscle pain.

2.15.3 Hypothyroidism

Observations of patients with chronic myalgia suggest that hypothyroidism is causally linked to MPS. Autoimmune thyroiditis occurs in FMS as well as in rheumatoid arthritis (Pamuk and Cakir 2007). Vitamin D deficiency also leads to thyroiditis. Myalgia is a manifestation of autoimmune thyroiditis (Punzi and Betterie 2004). There is as yet no epidemiological evidence that thyroid dysfunction is associated with MPS. Nevertheless, widespread symptomatic trigger points seem to appear in

some persons with MPS who are hypothyroid; such persons improve in endurance and report lessened pain when they are treated with thyroid supplementation. This observation awaits confirmation by a proper clinical trial. Underactive thyroid function is a form of hypometabolism, hence is consistent in view of the Expanded Integrated Theory of the Trigger Point (Simons et al. 1999, pp. 69–78; Gerwin et al. 2004). Thyroid hormone helps regulate the Na^+/K^+ ATPase pump, ion cycling, and thermogenesis (Guernesey and Edelman 1983; Beard et al. 1998).

Hypothyroidism has many potential causes, including decreased synthesis of thyrotropin-releasing hormone (TRH) or thyroid-stimulating hormone (TSH), autoimmune thyroiditis, and impaired conversion of tetraiodothyronine (T4) to triiodothyronine (T3). Conversion of inactive T4 to active T3 takes place by 5′-deiodination of T4 in the liver, and is an iron-requiring reaction (Sorvillo et al. 2003). Peripheral suppression of thyroid hormone activity occurs in "nonthyroidal illness syndrome," once known as the "sick euthryroid syndrome." Acute and chronic stress also suppresses the hypothalamic–pituitary–adrenal axis, resulting in central (hypothalamic) neuro-endocrine failure (Van den Berghe et al. 1998), decreased thyroid release of T4, and inhibition of 5′-deiodinase I (Feelders et al. 1999; Michalaki et al. 2001; Tsigos and Chrousos 2002). Proinflammatory cytokines IL-6 and tumor necrosis factor-alpha reduce TSH production and thyroid function (Witzke et al. 2001; Jakobs et al. 2002). Reverse T3 (rT3) is increased in the acute stress response. Decreased cortisol-releasing hormone (CRH) results in decreased glucocorticoid production and increases the likelihood of autoimmune disorders including thyroiditis.

The role of rT3-blocking of T3 activity is controversial. rT3 has been implicated in hormone-resistant hypothyroidism and in the development of myalgia (Garrison and Breeding 2003; Lowe 1997). Whether rT3 blocks the effect of T3 at the cellular level is unclear. In some situations, but not in all, rT3 has been found to be biologically active and capable of inhibiting T3 (Friberg et al. 2001; Martin et al. 2004). On the other hand, elevation of rT3 may simply be a nonspecific response of stress (Lange et al. 1999), and not have biologic activity. TSH may be normal even when rT3 levels are elevated and T3 activity may be diminished.

Statins are a known cause of myalgia and muscle necrosis, associated with elevations of CPK in more severe cases. Hypothyroidism is a risk factor for statin-induced myalgia. CPK elevation is more common in hypothyroid patients receiving statins than in persons who are euthyroid and receiving statins (Tokinaga et al. 2006).

There are as yet no studies that have definitively demonstrated a relationship between hypothyroidism and MPS, despite the apparent relationship clinically.

2.15.4 Iron Status and Thyroid Function

Iron-deficient rats have low plasma levels of active thyroid hormone T3, an impaired ability to convert inactive T4 to active T3, low levels of T4-5′ deiodinase

activity, low levels of TSH, and a dampened TSH response to TRH (Beard et al. 1989; Chiraseveenuprapund et al. 1978). The disposal rate of T4 and T3 (thyroid hormone kinetics) is lower in iron-deficient rats. However, thyroid hormone kinetics is normalized with thyroxine replacement, in the absence of changes in serum iron indices (Beard et al. 1998). The effect on thyroid hormone turnover has been postulated to be caused by impaired thermoregulatory responses in iron-deficient states (Beard et al. 1998). Iron-deficient individuals often complain of feeling cold. Iron-deficient rats are hypothermic, an effect related to the impaired conversion of T4–T3 (Dillman et al. 1980). Iron deficiency can adversely affect thyroid hormone metabolism (Arthur and Beckett 1999), but studies in humans give differing results. Goiter can be associated with iron deficiency (Azizi et al. 2002), but thyroid hormone levels and TSH responses have not been shown to be significantly different in iron-deficient populations (Yavuz et al. 2004; Tienboon and Unachak 2003). On the other hand, T3 augmentation can upregulate ferritin levels and increase iron-dependent functions (Leedman et al. 1996).

2.15.5 Vitamin D Deficiency

Vitamin D deficiency is associated with chronic, nonspecific musculoskeletal pain (Golan et al. 2009). A group of 150 consecutive individuals with the complaint of musculoskeletal pain, living in the northern United States, were evaluated for vitamin D status. The normal range of 25-hydroxy vitamin D (total vitamin D) is 32–80 ng/ml. Secondary hyperparathyroidism becomes increasingly common below levels of 18 ng/ml. In this study, 89% of the subjects had 25-OH vitamin D level of 20 mg/ml or less. Of the entire group, 28% had levels of 8 ng/ml or less, a severe deficiency (Plotnikoff and Quigley 2003). It is estimated that the prevalence of vitamin D deficiency ranges between 24% and 36%, irrespective of age or gender (Gordon et al. 2004; Tangpricha et al. 2002). A study of one clinic population in a winter climate found that 58% of new patients to the clinic were vitamin D-deficient (Bartley et al. 2009). A review of the vitamin D status in different regions of the world found widespread hypovitaminosis (Mithal et al. 2009).

Muscle weakness develops as a consequence of vitamin D deficiency (Bischoff et al. 1999; Bischoff et al. 2000; Janssen et al. 2002), particularly at levels below 30 ng/ml. Muscle mass is decreased in vitamin D-deficient animals. (Wassner et al. 1983; Simpson et al. 1985). Myofibrillar protein degradation occurs, and insulin levels are lower in vitamin-deficient rats than in normal rats. Vitamin D deficiency results in atrophy of type II muscle fibers (Sato et al. 2002). Fast-twitch type II muscle fiber number and cross-sectional diameter increase after treatment with 1-alpha-hydroxy-cholecalciferol, a vitamin D analog (Sorenson et al. 1979).

An indirect effect of vitamin D deficiency on muscle strength and bulk is mediated through parathyroid hormone (PTH), which is an increase in quantity in vitamin D deficiency. Increased PTH levels reduce energy production and utilization in muscle (Baczynski et al. 1985), increase intracellular free calcium

(Begum et al. 1992), and increase circulating levels of the cytokine IL6, which decreases muscle mass and causes weakness (Mitnick et al. 2001).

Vitamin D affects intracellular calcium levels, a factor that is thought to be related to the development of trigger points. Vitamin D activates several second messenger systems, including those that utilize tyrosine kinase and phospholipase C. Vitamin D stimulates the release of calcium from the sarcoplasmic reticulum through the voltage-dependent Ryanidine receptor, and also through activation of the protein kinase second messenger system (Mitnick et al. 2001; Buitrago et al. 2002; Santillan et al. 2004). The rate of calcium uptake into sarcoplasmic reticulum is decreased in vitamin D deficiency (Pointon et al. 1979). Excess intracellular calcium may contribute to persistent muscle contraction as is seen in the trigger point taut band.

Treatment with vitamin D supplementation is effective in reversing symptoms. Vitamin D is lipid-soluble, and is best absorbed when taken with a meal containing fat. It may not be well-absorbed in persons with adult celiac disease or other malabsorption states. Doses depend on the form of vitamin D taken. A single dose of 300,000 IU of vitamin D3 has been shown to be effective and maintain adequate levels for 6 months (von Restorff et al. 2009). More commonly, 50,000 IU of vitamin D3 is taken once weekly for 8 weeks followed by 400–2,000 IU of vitamin D2.

The data cited, that vitamin D deficiency is a cause of musculoskeletal pain and of muscle atrophy and weakness, are consistent with the concept that MTrP pain can occur with vitamin D deficiency, as we have seen in our practice. Vitamin D replacement has corrected the pain and weakness in these patients. However, there has been no controlled study of vitamin D in MPS, either to document a vitamin D deficiency or to evaluate the outcome in subjects taking vitamin D supplementation. At this time, recognizing that vitamin D deficiency is widespread and that it is associated with musculoskeletal pain and muscle atrophy, it is reasonable to obtain a serum 25-hydroxy vitamin D level (total vitamin D level), and to supplement with vitamin D when the level is 32 ng/ml or lower.

2.15.6 Statins

HMG-CoA reductase inhibitors (statins) are known to cause severe myopathy and rhabdomyolisis, albeit infrequently. However, myalgia can occur in the absence of elevated CPK levels. It is estimated that 1–5% of persons receiving statins develop muscle pain and weakness. Hypothyroidism, diabetes mellitus, and the use of certain medications such as gemfibrozil that increase statin plasma concentrations, increase the risk of development of myalgias. Nevertheless, there is no literature that relates statins specifically to the development of MPSs. Moreover, the role of statins in producing chronic myalgia, irrespective of trigger point formation, is controversial, because chronic myalgias have not been confirmed by blinded placebo-controlled trials (Brown 2008). However, it may be that both large numbers

and polypharmacy may be needed to identify this complication, and that may not be achieved with placebo-controlled trials.

2.15.7 Structural and Mechanical Factors

Biomechanical factors play a role in the development of MTrPs. Prolonged maintenance of posture may have the same effect as repeated low-level muscle activation cited above. Leg-length inequality and scoliosis likewise can produce chronic muscle overuse as compensatory mechanisms. Work-related muscle overload has been extensively studied and is discussed earlier in this chapter. Hypermobility has also been discussed earlier, and is another example of a mechanical dysfunction that causes chronic muscle overuse.

2.16 Selected Specific Clinical Syndromes

2.16.1 Headache

The most common headaches seen in clinical practice are tension-type headaches (TTH) and migraine (MH). The role of MTrPs in these headaches is either as the cause of pain through pain referred to the head from shoulder, neck, and head trigger points, tension-type headache, or activation of the trigeminovascular cascade by MTrPs in migraine, where referred pain also explains some of the headache patterns (Gerwin 2005). Trigger points in the trapezius muscle refer pain to the neck, the parietal area, and the temple. Trigger points in the SCM refer pain to the occiput, the vertex, the mastoid region, and the forehead. Suboccipital muscle and oblique capitis inferior muscle trigger points refer pain in a band-like fashion about the head, to the general region of the eye. Thus, referral patterns from trigger points in these muscles, and other head, neck, and shoulder muscles can produce the commonly seen headache patterns in TTH and in migraine without aura.

The role of MTrPs in the generation of headache has been intensively studied in recent years (Fernandez-de-las-Peñas et al. 2006a, 2006b, 2006c, 2007a, 2007b; Santiná and de Alenacar Júnior 2009). The general concept expounded in these series of papers is that chronic tension-type headache (CTTH) is at least partly explained by referred pain emanating from trigger points in the head, neck, and shoulder muscles. Trigger points are one factor leading to the development of the central sensitization that initiates referred pain and headache. Trigger points in the trochlear region have been identified in unilateral migraine headache (Fernandez-de-las-Peñas et al. 2005b, 2006d). Forward-head-postural dysfunction is associated with subocciptal muscle trigger points and chronic tension-type headache (Fernandez-de-las-Peñas et al. 2006c). Cross-sectional area of the rectus capitis

major and minor were both smaller in women with CTTH, but atrophy was not seen in the splenius or semispinalis muscles, and the rectus capitis posterior minor muscle was found to be selectively atrophic in women with active trigger points and chronic tension-type headache (Fernandez-de-las-Peñas et al. 2008b). It is not clear if this is a result of neck muscle trigger points or contributes to their development. Cervical muscle coactivation of antagonist muscles, a phenomenon present in MPSs, occurs in CTTH patients (Fernandez-de-las-Peñas et al. 2008c). Not surprisingly, trigger points in the temporalis muscle contribute to headache symptoms in CTTH (Fernandez-de-las-Peñas et al. 2006a, 2007b).

Key to the concept that trigger points contribute to the development of headache is the finding that treatment of relevant trigger points results in reduction or elimination of headache. This has been shown in one elegant study by Giamberadino et al. (2007), in which inactivation of trigger points that referred pain to the headache areas resulted in reduction of headache frequency and intensity, and a reduction in electrical pain thresholds. Another study, open labeled, showed that inactivation of trigger points in the head and neck by the injection of the long-acting local anesthetic ropivacaine decreased migraine headache frequency by more than 11% in more than 50% of subjects, and produced more than a 50% reduction in headache frequency in 17% of subjects (Garcia-Leiva et al. 2007). This study was problematic in that the authors talk about subcutaneous injection of trigger points, and not intramuscular injections. Moreover, there is no mention of postinjection assessment of the treated trigger points to evaluate the effectiveness of the injections. Outcome of CTTH improvement with muscle trigger point therapy was found to be directly related to the number of up to four variables such as headache duration, headache frequency, bodily pain, and "vitality," with over 80% likelihood of improvement if all four variables were present (Fernandez-de-las-Peñas et al. 2008a).

2.16.2 Fibromyalgia

There has long been a discussion about the relationship between myofascial pain and fibromyalgia, including whether myofascial pain evolves into fibromyalgia ("regional" pain evolving into "generalized" pain). Fibromyalgia is not a myalgic pain condition, however. It is a disorder of modulation of ascending nociceptive impulses, resulting in widespread pain amplification. It is characterized, however, by widespread musculoskeletal tenderness. Tender points are theoretically not associated with taut bands. However, MTrPs are also tender, and many clinicians do not make a distinction between taut bands and trigger points. There is, in fact, a major overlap between these two conditions. A preliminary report of 96 subjects evaluated for fibromyalgia and MPS found 25 subjects who fulfilled the criteria for fibromyalgia (Gerwin 1995). Of these, 18 (or 72%) had trigger points as well as tender points. Many of the sites that are examined as fibromyalgia tender points in fibromyalgia research studies in accordance with the American College of

Rheumatology criteria (Wolfe et al. 1990) have MTrPs in fibromyalgia. Furthermore, many of the comorbidities of fibromyalgia, such as headache and chronic pelvic pain, can be the result of trigger point pain syndromes, such as pelvic floor muscle dysfunctions. Central and peripheral hypersensitization is considered to be the basis of fibromyalgia. It is also implicated in the etiology of MPS. There is interest, therefore, in whether persons with fibromyalgia have MTrPs that account for the pain of fibromyalgia.

2.16.3 Endometriosis and Other Pelvic Viscerosomatic Pain Syndromes

Chronic pelvic pain (CPP) affects both men and women. It usually affects the lower abdomen, but also affects the perineal region, interfering with sitting, walking, and standing. It is a manifestation of a variety of visceral pain syndromes, including disorders of the reproductive organs, the bowel, and the ureters and bladder. However, it has been termed a condition that cannot be explained medically, but a condition that is longstanding (Weijenborg et al. 2007). Nevertheless, CPP can also be a manifestation of pelvic floor muscle dysfunction. It occurs with a prevalence of 14–24% in women of reproductive age, but a prevalence of 3–4% in primary care (Weijenborg et al. 2007). Seventy-five percent of women with chronic pelvic pain continued to have significant pain at a mean follow-up period of 3.4 years. The association of CPP with body wall muscle pain, including the pelvic floor muscles, appears to be high, although no figures are available. An example of this association is the abdominal muscle hyperalgesia that is induced by a ureteral calculosis (Giamberardino et al. 2002). The mechanism that has been postulated is sensitization of convergent viscero-somatic sensory neurons in the spinal cord dorsal horn, emphasizing the role of hyperalgesia in viscero-somatic pain syndromes (Giamberardino 2000). A treatment program emphasizing a multidisciplinary approach that includes assessment and treatment of myofascial pain as well as medication, surgery where appropriate, physical therapy, and cognitive/psychological management has been recommended by the Society of Obstetrics and Gynecology of Canada (Jarrell et al. 2005).

The patient with CPP is evaluated for mechanical musculoskeletal dysfunction such as sacroiliac joint hypomobility, pubic symphysis off-set, and pelvic asymmetries that can lead to mechanical muscle stress and trigger point development. When found, these problems should be corrected when possible. The muscles that can produce pelvic region pain include the psoas and iliacus muscles, which can cause back and groin pain. The quadratus lumborum can refer pain into the lower abdominal quadrant and into the hip region. Trigger points in gluteal muscles can refer pain to the hip, simulating trochanteric bursitis, to the sacrum and sacroiliac joints, and down the leg, simulating radiculitis. Obturator internus muscle trigger points refer pain to the groin, to the perianal region, and to the trochanteric region. Piriformis muscle trigger points can not only refer pain to the hip, buttocks and

postero-lateral thigh, but can also entrap the sciatic nerve, causing pain that looks like L5 or S1 radiculopathy. The levator ani can develop trigger points that are chronically painful and that cause pain on sitting. Vaginal pain can be felt with these pain syndromes. Pain that is localized to the ischial tuberosity can make sitting painful. This kind of pain is often caused by trigger points in the upper medial hamstring muscles and the adductor magnus muscle. Adductor magnus trigger points can also cause a diffuse, deep intra-pelvic pain.

Recurrent abdominal pain is a common manifestation in endometriosis, a serious pelvic pain problem. Endometriosis is often managed with laparoscopic surgical procedures when hormonal control is not effective in order to identify and remove endometrial implants and to lyse adhesions. However, abdominal pain often recurs, necessitating repeated laparoscopic surgical procedures. Moreover, surgical excision of endometrial implants does not result in an improvement of 1-year outcome compared to sham surgery (Jarrell et al. 2005). However, the cause of pain may not be the endometriosis itself, but abdominal wall trigger points that may represent pain referral from the affected viscera, or even may reflect the development of trigger points from the surgical procedure itself (Srinivasan and Greenbaum 2002; Jarrell and Robert 2003; Nazareno et al. 2005). Jarrell (Jarrell 2004, 2008; Jarrell and Robert 2003) found that treating abdominal trigger points alleviated the visceral pain syndromes. However, Nazareno (Nazareno et al. 2005) did not define MTrPs; it is not clear what criteria he used to direct his choice of injection site in the abdominal wall other than tenderness. He reported an 89% partial or complete relief of pain both short and long term, with no apparent greater benefit following the addition of corticosteroids to the injection mixture. Another study examined the results of treatment of abdominal pain with point tenderness following surgery or diagnosed with abdominal adhesions, pelvic inflammatory disease, or nerve entrapment (Kuan et al. 2006). Treatment was by injection of local anesthetic and corticosteroids into trigger points (the paper did not define how they were defined or localized). The authors reported 95% of 140 treated patients were either pain free or had only mild pain after treatment, and that the benefit was sustained for 3 months (86.5% retained the benefit).

Treatment of pelvic pain associated with interstitial cystitis responded to pelvic floor muscle trigger point treatment in a report of a small case series (Doggweiler-Wiygul and Wiygul 2002). Pelvic floor pain syndromes and pelvic visceral pain syndromes such as noninfectious prostatitis, levator ani syndrome, irritable bowel syndrome, and interstitial cystitis commonly have pelvic floor and abdominal wall trigger points relevant to the complaint of pain, but are poorly understood (Srivivasan et al. 2007).

2.16.4 Radiculopathy

MTrP pain may be the presenting symptom and the only sign of cervical or lumbar radiculopathy in some patients. This phenomenon has not been well-described in

the literature, but certainly opens the question of the relationship between root compression and the development of trigger points, and of the nature of at least a component of pain in radicular syndromes. In one study, 191 subjects evaluated for suspected cervical radiculopathy were evaluated for MPS as well as for other conditions (Cannon et al. 2007). Electrodiagnostic testing identified cervical radiculopathy in 52% of subjects, and other neurological syndromes (plexopathy, peripheral nerve entrapments, or polyneuropathy) in 25%. MPS was found in 53% of persons with normal electrodiagnostic testing, and also in 17% of patients with electrodiagnostic evidence of radiculopathy and 19% of those with other nerve diagnoses. Although diagnostic criteria for the identification of MTrP pain were not well defined in this study, the authors nevertheless highlight both the possibility that MPSs may mimic cervical radiculopathy, and may be a symptomatic comorbidity of cervical radiculopathy. Moreover, the author has found that many patients with postlaminectomy pain syndromes have MTrP pain syndromes rather than recurrent disc herniation or scar formation. These findings have not been explored either in the literature.

2.16.5 Thoracic Outlet Syndrome

Thoracic outlet syndrome (TOS) is a controversial condition affecting the arm, shoulder, and neck. The principle symptoms are pain with use of the limb, or even at rest in severe cases. Numbness and paresthesias can occur, usually in the distribution of the ulnar nerve, but the whole hand can be affected. True neurogenic TOS occurs as a result of compression of the brachial plexus somewhere between the neck and the shoulder. When symptoms occur with elevation of the arm, the condition is referred to as hyperabduction syndrome. Vascular TOS occurs when the vascular bundle is compressed, and represents a form of intermittent claudication of the upper extremity, sometimes accompanied by emboli to the fingers. True neurogenic TOS can be caused by stretching of the lower nerve roots or trunk of the brachial plexus by a cervical rib or a ligamentus band from an elongated transverse process to the first rib. The condition is rare. The more common presentation of TOS-like pain and paresthesias not associated with definite neurologic impairment has been termed ‘disputed TOS’ or ‘nonspecific TOS’ because it is not associated with any definable nerve compression.

The role of MTrPs in nonspecific TOS is twofold. Entrapment of the brachial plexus can occur in the interscalene compartment by trigger points in the medial and anterior scalene muscles which compress and narrow the interscalene compartment and its contents. Entrapment of the neurovascular bundle can also occur as it passes between the clavicle and the first rib. Shortening of the anterior and medial scalene muscles by MTrPs elevates the first rib, narrowing the space between the rib and the clavicle. Shortening of the pectoralis minor muscle by trigger points compresses the neurovascular bundle which passes deep to the muscle that attaches to the coracoid process, particularly when the arm is abducted. The second aspect of

trigger point relationship to TOS is the mimicking of TOS symptoms of pain by referred pain from trigger points in the shoulder muscles, including the scalenes, the infra- and supra-spinatus, the levator scapula, the subscapularis, and the latissimus dorsi muscles. These muscles all refer pain in the shoulder and down the arm. Muscle trigger points can thus create nerve compression and also cause pain referral patterns in the distribution of the compressed nerve. In this sense, nonspecific TOS is better called myogenic TOS, to reflect the role of muscle in this syndrome.

2.17 Conclusion

Research in myofascial pain has increased greatly since the basis for peripheral and central nervous system sensory sensitization became established. Much of the work on pain mechanisms in muscle and the effects of neural sensitization, such as the expansion of receptive fields, has been done by Mense and his associates. Many clinical studies were done by Hong and his group both in the United States and in Taiwan. David Simons was often the catalyst, if not the investigator, in many studies that established the nature of the disorder in the trigger point dysfunction. The work of these individuals and others laid the groundwork for further studies that have been now forthcoming in ever increasing numbers. The advent of more sophisticated imaging allows new ways of evaluating both the muscle harboring a trigger point and central responses to muscle trigger point pain. Nevertheless, there are many areas that need more detailed or innovative studies in order to expand our knowledge about the fundamental nature of the trigger point as well as to develop more effective ways of diagnosing and managing trigger point-related pain. It is hoped that the comments in this chapter will direct attention to some of the areas that await further attention from those interested in the nature of muscle pain and in ways to alleviate it.

References

Adib N, Davies K, Grahame R et al. (2005) Joint hypermobility syndrome in childhood. A not so benign multisystem disorder? Rheumatology 44:744–750

Andersen LL, Holtermann A, Jørgensen MB et al. (2008a) Rapid muscle activation and force capacity in conditions of chronic musculoskeletal pain. Clin Biomech 23(10):1237–1242

Andersen LL, Suetta C, Andersen JL et al. (2008b) Increased proportion of megafibers in chronically painful muscles. Pain 139:588–593

Arendt-Nielsen L, Sluka KA, Nie HL (2008a) Experimental muscle pain impairs descending inhibition. Pain 140:465–471

Arendt-Nielsen L, Svensson P, Sessle BJ et al. (2008b) Interactions between glutamate and capsaicin in inducing muscle pain and sensitization in humans. Eur J Pain 12(5):661–670

Armstrong RB, Oglive RW, Schwane JA (1983) Eccentric exercise-induced injury to rat skeletal muscle. J Appl Physiol 54:80–93

Arthur JR, Beckett GJ (1999) Thyroid function. Br Med Bull 55:658–668

Azizi F, Mirmiran P, Sheikholeslam R et al. (2002) Int J Vitam Nutr Res 72:296–299
Baczynski R, Massry SG, Maggot M et al. (1985) Effect of parathyroid hormone on energy metabolism of skeletal muscle. Kidney Int 2:722–727
Badley EM, Webster GK, Rasooly I (1995) The impact of musculoskeletal disorders in the population: are they just aches and pains? Findings from the 1990 Ontario Health Survey. J Rheumatol 22:733–739
Baldry P (2002) Management of myofascial trigger point pain. Acupunct Med 20:2–10
Barbe MF, Elliott MB, Abdelmagid SM et al. (2008) Serum and tissue cytokines and chemokines increase with repetitive upper extremity tasks. J Orthop Res 26:1320–1326
Bartley J, Reid D, Morton RP (2009) Prevalence of vitamin D deficiency among patients attending a general otolaryngology clinic in South Auckland. Ann Otol Rhinol Laryngol 118:326–328
Beard J, Tobin B, Green W (1989) Evidence for thyroid deficiency in iron-deficient anemic rats. J Nutr 119:772–778
Beard JL, Brigham DE, Kelley SK et al. (1998) Plasma thyroid hormone kinetics are altered in iron-deficient rats. J Nutr 128:1401–1408
Begum N, Sussman KE, Draznin B (1992) Calcium-induced inhibition of phosphoserine phosphotase in insulin target cells is mediated by the phosphorylation and activation of inhibitor 1. J Biol Chem 267:5959–5963
Beighton P, Solomon L, Soskolne CL (1973) Articular mobility in an African population. Ann Rheum Dis 32:413–418
Bergenudd H, Lindgärde F, Nilsson B et al. (1988) Shoulder pain in middle age. A study of prevalence and relation to occupational work load and psychosocial factors. Clin Orthop 231:234–238
Bird GC, Han JS, Fu Y et al. (2006) Pain-related synaptic plasticity in spinal dorsal horn neurons: role of CGRP. Mol Pain 2:31
Bischoff HA, Stahelin HB, Urscheler N et al. (1999) Muscle strength in the elderly: its relation to vitamin D metabolites. Arch Phys Med Rehab 80:54–58
Bischoff HA, Stahelin HB, Tyndall A et al. (2000) Relationship between muscle strength and vitamin D metabolites: are there therapeutic possibilities in the elderly? Z. Rheumatology 59 (Suppl 1):39–41
Brigham DE, Beard JL (1995) Effect of thyroid hormone replacement in iron-deficient rats. Am J Physiol 269(5 Pt 2):R1140–1147
Brinkert W, Dimcevski G, Arendt-Nielsen L et al. (2007) Dysmenorrhea is associated with hypersensitivity in the sigmoid colon and rectum. Pain 132(Suppl 1):S46–S51
Bron C, Franssen J, Wensing M et al. (2007) Interrater reliability of palpation of myofascial trigger points in three shoulder muscles. J Man Manip Ther 15:203–215
Brown WV (2008) Safety of statins. Curr Opin Lipidol 19:558–562
Brückle W, Suckfüll M, Fleckenstein W et al. (1990) Gewebe-pO2-Messung in der verspannten Rückenmuskulatur (m. erector spinae). Z Rheumatol 49:208–216
Buitrago C, Gonzálos Pardo V, de Boland AR (2002) Nongenomic action of 1 alpha, 25(OH)(2)-vitamin D3. Activation of muscle cell PLC gamma through the tyrosine kinase s-SRC and Ptdlns 3-kinase. Eur J Biochem 269:2506–2515
Bujak DI, Weinstein A, Dornbush RI (1996) Clinical and neurocognitive features of the post-Lyme syndrome. J Rheumatol 23:1392–1397
Cairns BE, Gambarota G, Svensson P et al. (2002) Glutamate-induced sensitization of rat muscle fibers. Neuroscience 16:105–117
Cannon DE, Dillingham TR, Miao H et al. (2007) Musculoskeletal disorders in referral for suspected cervical Radiculopathy. Arch Phys Med Rehabil 88:1256–1259
Centers for Disease Control and Prevention (1995) Recommendations for test performance and interpretation from the Sencon International Conference on serologic diagnosis of Lyme disease. MMWR Morb Mortal Wkly Rep 44:1

Chaiamnuay P, Darmawan J, Muirden KD et al. (1998) Epidemiology of rheumatic disease in rural Thailand: a WHOILAR COPCORD study. Community Oriented Program for the Control of Rheumatic Disease. J Rheumatol 25:1382–1387

Chang CW, Chen YR, Chang KF (2008) Evidence of neuroaxonal degeneration in myofascial pain syndrome: a study of neuromuscular jitter by axonal microstimulation. Eur J Pain 12:1026–1030

Chen JT, Chen SM, Kuan TS et al. (1998) Phentolamine effect on the spontaneous electrical activity of active loci in a myofascial trigger spot of rabbit skeletal muscle. Arch Phys Med Rehab 79:790–794

Chen SM, Chen JT, Kuan TS et al. (2000) Decrease in pressure pain thresholds of latent myofascial trigger points in the middle finger extensors immediately after continuous piano practice. J Musculoskelet Pain 8((3):83–92

Chen Q, Bensamoun S, Basford J et al. (2007) Identification and quantification of myofascial taut bands with magnetic resonance elastography. Arch Phys Med Rehabil 88:1658–1661

Chen Q, Basford J, An K-N (2008) Ability of magnetic resonance elastography to assess taut bands. Clin Biomech 23:623–629

Chiraseveenuprapund P, Buergi U, Goswami A et al. (1978) Conversion of L-thyroxine to triidothyronine in rat kidney homogenate. Endocrinology 102:612–622

Christidis N, Kopp S, Ernber M (2005) The effect on mechanical pain threshold over human muscles by oral administration of granisetron and diclofenic-sodium. Pain 113:265–270

Cooper CE (1999) Nitric oxide and iron proteins. Biochim Biophys Acta 1411:290–309

Cummings TM, White AR (2001) Needling therapies in the management of myofascial trigger point pain: a systematic review. Arch Phys Med Rehabil 82:986–992

Dannecker EA (2008) Sex-related differences in delayed-onset muscle pain. In: Graven-Nielsen T, Arendt-Nielsen L, Mense S (eds) Fundamentals of musculoskeletal pain. IASP, Seattle

Dannecker EA, Knoll V, Robinson ME (2008) Sex differences in muscle pain: self-care behaviors and effects on daily activities. J Pain 9:200–209

DeSantanta JM, Sluka KA (2008) Central mechanisms in the maintenance of chronic widespread noninflammatory muscle pain. Curr Pain Headache Rep 12:338–343

Dillman E, Gale C, Green W et al. (1980) Hypothermia in iron deficiency due to altered triiodothyronine metabolism. Am J Physiol 239:R377–R381

Dina OA, Levine JD, Green PG (2008) Muscle inflammation induces a protein kinase Cε-dependent chronic-latent muscle pain. J Pain 9:457–462

Doggweiler-Wiygul R, Wiygul JP (2002) Interstitial cystitis, pelvic pain, and the relationship to myofascial pain and dysfunction: a report on four patients. World J Urol 20:310–314

Dommerholt J, Bron C, Franssen J (2006a) Myofascial trigger points: an evidence-informed review. J Man Manip Ther 14:203–221

Dommerholt J, Mayoral del Moral O, Gröbli C (2006b) Trigger point dry needling. J Man Manip Ther 14:E70–E87

Donta ST (2003) Macrolide therapy of chronic Lyme disease. Med Sci Monit 9:P1136–P1142

Dumitru D, King JC, Stegeman DF (1998) Endplate spike morphology: a clinical and simulation study. Arch Phys Med Rehabil 79:634–640

Dundar U, Evcik D, Samli F et al. (2007) The effect of gallium arsenide aluminum laser therapy in the management of cervical myofascial pain syndrome: a double blind, placebo-controlled study. Clin Rheumatol 26:930–934

Editor's note to authors and readers (2009) Levels of evidence. Neurology 72:109

Edwards CA, Bowyer JR, Trumpower BL (1982) Function of the iron-sulfur protein of the cytochrome b-c_1 segment in electron transfer reactions of the mitochondrial respiratory chain. J Biol Chem 257:3705–3713

Elliott MB, Barr AE, Clark BD et al. (2009) High force reaching task induces widespread inflammation, increased spinal cord neurochemicals and neuropathic pain. Neuroscience 158:922–931

El-Metwally A, Jouko JS, Auvinen A et al. (2004) Prognosis of non-specific musculoskeletal pain in preadolescents: a prospective 4 year follow-up study till adolescence. Pain 110:550–559

Ernberg M (2008) Serotonergic receptor involvment in muscle pain and hyperalgesia. In: Graven-Nielsen T, Arendt-Nielsen L, Mense S (eds) Fundamentals of musculoskeletal pain. IASP Press, Seattle

Farina D, Leclerc F, Arendt-Nielsen L et al. (2008) The change in spatial distribution of upper trapezius muscle activity is correlated to contraction duration. J Electromyogr Kinesiol 18:16–25

Feelders RA, Swank AJ, Romijn JA et al. (1999) Characteristic of recovery from euthyroid sick syndrome induced by tumor necrosis factor alpha in cancer patients. Metabolism 48:324–329

Fernandez-Carnero J, Fernandez-de-las-Peñas C, de la Llave-Rincón I et al. (2008) Bilateral myofascial trigger points in the forearm muscles in patients with chronic unilateral epicondylalgia: a blinded, controlled study. Clin J Pain 24:802–807

Fernandez-de-las-Peñas C, Campo MS, Carnero JF et al. (2005a) Manual therapies in the myofascial trigger point treatment: a systematic review. J Bodyw Mov Ther 9:27–35

Fernandez-de-las-Peñas C, Cuadrado RD, Gerwin RD et al. (2005b) Referred pain from the trochlear region in tension-type headache: a myofascial trigger point from the superior oblique muscle. Headache 45:731–737

Fernandez-de-las-Peñas C, Fernández J, Miangolarra JC (2005c) Musculoskeletal disorders in mechanical neck pain: myofascial trigger points versus cervical joint dysfunctions. A clinical study. J Musculoskel Pain 13:27–35

Fernandez-de-las-Peñas C, Palonecque del Cerro L, Fernandez Carnero J (2005d) Manual treatment of post-whiplash injury. J Bodyw Mov Ther 9:109–119

Fernandez-de-las-Peñas C, Arendt-Nielsen L, Simons DG (2006a) Contributions of myofascial trigger points to chronic tension type headache. J Man Manip Ther 14:222–231

Fernandez-de-las-Peñas C, Alonso-Blanco C, Alguacil-Diego IM et al. (2006b) Myofascial trigger points and postero-anterior joint hypomobility in the mid-cervical spine in subjects presenting with mechanical neck pain: a pilot study. J Man Manip Ther 14:88–94

Fernandez-de-las-Peñas C, Alonso-Blanco C, Cuadrado ML et al. (2006c) Trigger points in the suboccipital muscles and forward head posture in tension-type headache. Headache 46:454–460

Fernandez-de-las-Peñas C, Cuadrado ML, Gerwin RD et al. (2006d) Myofascial disorders in the troclear region in unilateral migraine. Clin J Pain 22:548–553

Fernandez-de-las-Peñas C, Cuadrado ML, Arendt-Nielsen L et al. (2007a) Myofascial trigger points and sensitization: an updated pain model for tension-type headache. Cephalalgia 27:383–393

Fernandez-de-las-Peñas C, Ge HY, Arendt-Nielsen L et al. (2007b) The local and referred pain from myofascial trigger points in the temporalis muscle contributes to pain profile in chronic tension-type headache. Clin J Pain 23:786–792

Fernandez-de-las-Peñas C, Cleland JA, Cuadrado ML et al. (2008a) Predictor variables for identifying patients with chronic tension-type headache who are likely to achieve short-term success with muscle trigger point therapy. Cephalalgia 28:264–275

Fernandez-de-las-Peñas C, Cuadrado ML, Arendt-Nielsen L et al. (2008b) Association of cross-sectional area of the rectus capitis posterior minor muscle with active trigger points in chronic tension-type headache: a pilot study. Am J Phys Med Rehabil 87:197–203

Fernandez-de-las-Peñas C, Falla D, Arendt-Nielsen L et al. (2008c) Cervical muscle co-activation in isometric contractions is enhanced in chronic tension-type headache patients. Cephalalgia 28:744–751

Ferrante FM, Bearn L, Rothrock R et al. (2005) Evidence against trigger point injection technique for the treatment of cervicothoracic myofascial pain with botulinum toxin type A. Anesthesiology 103:377–383

Ferrell WR, Tennant N, Sturrock RD et al. (2004) Amelioration of symptoms by enhancement of proprioception in patients with joint hypermobility syndrome. Arthritis Rheum 50:3323–3328

Filosto M, Tonin P, Vattemi G et al. (2007) The role of muscle biopsy in investigating isolated muscle pain. Neurology 68:181–186
Fine PG, Milano R, Hare BD (1988) The effects of myofascial trigger point injections are naloxone reversible. Pain 32:15–20
Fischer AA (1987) Tissue compliance meter for objective, quantitative documentation of soft tissue consistency and pathology. Arch Phys Med Rehabil 68:122–125
Fischer AA (1988) Documentation of myofascial trigger points. Arch Phys Med Rehabil 69:286–291
Fischer AA (1997) New developments in diagnosis of myofascial pain and fibromyalgia. Phys Med Rehabil Clin North Am 8:1–21
Fishbain DA, Goldberg M, Meagher BR et al. (1986) Male and female chronic pain patients categorized by DS-III psychiatric diagnostic criteria. Pain 26:181–197
Frey Law LA, Evans S, Knudtson J et al. (2008a) Massage reduces pain perception and hyperalgesia in experimental muscle pain: a randomized, controlled trial. J Pain 9:714–721
Frey Law LA, Sluka KA, McMullen T et al. (2008b) Acidic buffer induced muscle pain evokes referred pain and mechanical hyperalgesia in humans. Pain 140:254–264
Friberg L, Drvota V, Bjelak AH et al. (2001) Association between increased levels of reverse triiodothyronine and mortality after acute myocardial infarction. Am J Med 111:699–703
Fryer G, Hodgson L (2005) The effect of manual pressure release on myofascial trigger points in the upper trapezius muscle. J Bodyw Mov Ther 9:248–255
Fujii Y, Ozaki N, Taguchi T et al. (2008) TRP channels and ASICs mediate mechanical hyperalgesia in models of inflammatory muscle pain and delayed onset muscle soreness. Pain 140:292–304
Furlan AD, Brosseau L, Imamura M et al. (2002) Massage for low-back pain: a systematic review with the framework of the Cochrane Collaboration Back Review Group. Spine 27:1896–1910
Ga H, Ko HJ, Choi JH et al. (2007a) Intramuscular and nerve root stimulation vs lidocaine injection of trigger points in myofascial pain syndrome. J Rehabil Med 39:374–378
Ga H, Choi JH, Yoon HY (2007b) Dry needling of trigger points with and without paraspinal needling in myofascial pain syndromes in elderly patients. J Altern Compl Med 13:617–623
Gam AN, Warming S, Larsen LH et al. (1998) Treatment of myofascial trigger-points with ultrasound combined with massage and exercise — a randomized controlled trial. Pain 77:73–79
Gandhi R, Ryals JM, Wright DE (2004) Neurotrophin-3 reverses chronic mechanical hyperalgesia induced by intramuscular acid injection. J Neurosci 24:9405–9413
Garcia-Leiva JM, Hildago J, Rico-Villademoros F et al. (2007) Effectiveness of Ropivacaine trigger points inactivation in the prophylactic management of patients with severe migraine. Pain Med 8:65–70
Garrison RL, Breeding PC (2003) A metabolic basis for fibromyalgia and its related disorders: the possible role of resistance to thyroid hormone. Med Hypotheses 61:182–189
Ge HY, Arendt-Nielsen L, Farini D et al. (2005) Gender-specific differences in electromyographic changes and perceived pain induced by experimental muscle pain during sustained contractions of the upper trapezius muscle. Muscle Nerve 32:726–733
Ge HY, Madeleine P, Cairns BE et al. (2006) Hypoalgesia in the referred pain areas after bilateral injections of hypertonic saline into the trapezius muscles of men and women: a potential experimental model of gender-specific differences. Clin J Pain 22:37–44
Gedalia A, Press J, Klein M et al. (1993) Joint hypermobility and fibromyalgia in schoolchildren. Ann Rheum Dis 52:494–496
Gerdle B, Hilgenfeldt U, Larsson B et al. (2008a) Bradykinin and kallidin levels in patients with work-related trapezius myalgia, in patients with whiplash associated pain, and in healthy controls — a microdialysis study of women. Pain 139:578–587
Gerdle B, Lemming D, Kristiansen J et al. (2008b) Biochemical alterations in the trapezius muscle of patients with chronic whiplash associated disorders (WAD) — a microdialysis study. Eur J Pain 12:82–93

Gerwin RD (1995) A study of 96 subjects examined both for fibromyalgia and myofascial pain. J Musculoskel Pain 3(Suppl 1):121
Gerwin RD, Dommerholt J (2001) unpublished data
Gerwin R (2005) Headache. In: Ferguson LW, Gerwin R (eds) Clinical mastery in the treatment of myofascial pain. Lippincott Williams & Wilkins, Philadelphia
Gerwin RD (2008) The taut band and other mysteries of the trigger point: an examination of the mechanisms relevant to the development and maintenance of the trigger point. J Musculoskelet Pain 15(Suppl 13):115–121
Gerwin RD, Duranleau D (1997) Ultrasound identification of the myofascial trigger point. Muscle Nerve 20:767–776
Gerwin RD, Shannon S, Hong CZ et al. (1997) Interrater reliability in myofascial trigger point examination. Pain 69:65–73
Gerwin RD, Dommerholt J, Shah J (2004) An expansion of Simons' integrated hypothesis of trigger point formation. Curr Pain Headache Rep 8:468–475
Giamberadino MA, Tafuri E, Savini A et al. (2007) Contribution of myofascial trigger points to migraine symptoms. J Pain 8:869–878
Giamberardino MA (2000) Sex-related and hormonal modulation of visceral pain. In: Fillingim RB (ed) Progress in pain research and management, vol 17. IASP, Seattle
Giamberardino MA, Berkley KJ, Affaitati G et al. (2002) Influence of endometriosis on pain behaviors and muscle hyperalgesia induced by a ureteral calculosis in female rats. Pain 95:247–257
Gibson W, Arendt-Nielsen L, Graven-Nielsen T (2006) Referred pain and hyperalgesia in human tendon and muscle belly tissue. Pain 120:113–123
Golan E, Haggiag I, Os P et al. (2009) Calcium, parathyroid hormone, and vitamin D: major determinants of chronic pain in hemodialysis patients. Clin J Am Soc Nephrol 4:1374–1380
Gordon CM, DePeter KC, Feldman HA et al. (2004) Prevalence of vitamin D deficiency among healthy adolescents. Arch Pediatr Adolesc Med 150:323–328
Grahame R (2000) Pain, distress and joint hyperlaxity. Joint Bone Spine Rev Rheum 67:157–163
Graven-Nielsen T, Arendt-Nielsen L (2008) Human models and clinical manifestations of musculoskeletal pain and pain-motor interactions. In: Graven-Nielsen T, Arendt-Nielsen L, Mense S (eds) Fundamentals of musculoskeletal pain. IASP, Seattle
Graven-Nielsen T, Mense S (2001) The peripheral apparatus of muscle pain: evidence from animal and human studies. Clin J Pain 17:2–10
Guernesey DL, Edelman IS (1983) Regulation of thermogenesis by thyroid hormones. In: Oppenheimer JH, Samuels HH (eds) Molecular basis of thyroid hormone action. Academic, New York
Gur A, Sarac AJ, Cevik R et al. (2004) Efficacy of 904 nm gallium arsenide low level laser therapy in the management of chronic myofascial pain in the neck: a double-blind and randomized-controlled trial. Lasers Surg Med 35:229–235
Hägg GM (2003) The Cinderella hypothesis. In: Johansson H et al. (eds) Chronic work-related myalgia. Gävle University Press, Gävle, Sweden
Harris AJ, Duxson MJ, Butler JE et al. (2005) Muscle fiber and motor unit behavior in the longest human skeletal muscle. J Neurosci 25:8528–8533
Ho K-Y, Tan K-H (2007) Botulinum toxin A for myofascial trigger point injection: a qualitative systematic review. Eur J Pain 11:519–527
Hoheisel U, Reinohl J, Unger T et al. (2004) Acidic pH and capsaicin activate mechanosensitive group IV muscle receptors in the rat. Pain 110:149–157
Hong CZ (1994) Persistence of local twitch response with loss of conduction to and from the spinal cord. Arch Phys Med Rehabil 7:12–16
Hong CZ, Simons DG (1998) Pathophysiologic and electrophysiologic mechanisms of myofascial trigger points. Arch Phys Med Rehabil 79:863–872
Hong CZ, Torigoe Y (1994) Electrophysiologic characteristics of localized twitch responses in responsive taut bands of rabbit skeletal muscle. J Musculoskelet Pain 2:17–43

Hong CZ, Yu J (1998) Spontaneous electrical activity of rabbit trigger spot after transection of spinal cord and peripheral nerve. J Musculoskelet Pain 6:45–58
Hong CZ, Torigoe Y, Yu J (1995) The localized twitch responses in responsive taut bands of rabbit skeletal muscle fibers are related to the reflexes at spinal cord level. J Musculoskelet Pain 3(1):15–33
Hou CR, Chung KC, Chen JT, Hong CZ (2002) Effects of a calcium channel blocker on electrical activity in myofascial trigger spots of rabbits. Am J Phy Med Rehabil 81:342–349
Hsieh YL, Kao MJ, Kuan TS et al. (2007) Dry needling to a key myofascial trigger point may reduce the irritability of satellite MTrPs. Am J Phys Med Rehabil 86:397–403
Hubbard DR, Berkoff GM (1993) Myofascial trigger points show spontaneous needle EMG activity. Spine 18:1803–1807
Hucho TB, Dina OA, Kuhn J, Levine JD (2006) Estrogen controls PKCepsilon-dependent mechanical hyperalgesia through direct action on nociceptive neurons. Eur J Neurosci 24:527–534
Hudson N, Starr MR, Esdaile JM et al. (1995) Diagnostic association with hypermobility in rheumatology patients. Br J Rheumatol 34:1157–1161
Hudson N, Fitzcharles MA, Cohen M et al. (1998) The association of soft-tissue rheumatism and hypermobility. Br J Rheumatol 37:382–386
Hwang M, Kang YK, Kim DH (2005a) Referred pain pattern of the pronator quadratus muscle. Pain 116:238–242
Hwang M, Kang JK, Shin JY, Kim DH (2005b) Referred pain pattern of the abductor pollicus longus muscle. Am J Phys Med Rehabil 84:593–597
Ilbuldu E, Cakmak A, Disci R et al. (2004) Comparison of laser, dry needling and placebo laser treatments in myofascial pain syndrome. Photomed Laser Surg 22:306–311
Irnich D, Behrens N, Gleditsch JM et al. (2002) Immediate effects of dry needling and acupuncture at distant points in chronic neck pain: results of a randomized, double-blind, sham-controlled crossover trial. Pain 99:83–89
Isselee H, De Laat A, De Mot B et al. (2002) Pressure–pain threshold variation in temporomandibular disorder myalgia over the course of the menstrual cycle. J Orofac Pain 16:105–117
Itoh K, Katsumi Y, Kitakoji H (2004) Trigger point acupuncture treatment of chronic low back pain in elderly patients – a blinded RCT. Acupunct Med 22:170–177
Itoh K, Katsumi Y, Hirota S et al. (2006a) Effects of trigger point acupuncture on chronic low back pain in elderly patients — a sham-controlled randomized trial. Acupunct Med 24:5–12
Itoh K, Katsumi Y, Hirota S et al. (2006b) Randomized trial of trigger point acupuncture compared with other acupuncture for treatment of chronic neck pain. Compl Ther Med 15:172–179
Iwama H, Ohmori S, Kaneko T et al. (2001) Water-diluted local anesthetic for trigger-point injection in chronic myofascial pain syndrome: evaluation of types of local anesthetic and concentrations in water. Reg Anesth Pain Med 26:333–336
Jacobsen S, Bartels EM, Dammeskiold-Samsøe B (1991) Single cell morphology of muscle in patients with chronic muscle pain. Scand J Rheumatol 20:336–343
Jakobs JL, Mentrup B, Schmutzler C et al. (2002) Proinflammatory cytokines inhibit the expression and function of human type I 5'deiodinase in HepG2 hepatocarcinoma cells. Eur J Endocrinol 14:559–566
Jang JU, Nam TS, Paik KS et al. (2004) Involvement of peripherally released substance P and calcitonin gene-related peptide in mediating mechanical hyperalgesia in a traumatic neuropathy model of the rat. Neurosci Lett 360:129–132
Janssen HC, Samson MM, Verhaar HJ (2002) Vitamin D deficiency, muscle function, and falls in elderly people. Am J Clin Nutr 75:611–615
Jarrell J (2004) Myofascial dysfunction in the pelvis. Curr Pain Headache Rep 8:452–456
Jarrell J (2008) Gynecological pain, endometriosis, visceral disease, and the viscero-somatic connection. J Musculoskelet Pain 16(1/2):21–27
Jarrell J, Robert M (2003) Myofascial dysfunction and pelvic pain. Can J CME:107–116
Jarrell JF, Vilos GA, Allaire C et al. (2005) Consensus guidelines for the management of chronic pelvic pain. J Obstet Gynaecol Can 27:781–826

Johansen MK, Graven-Nielsen T, Olesen AS et al. (1999) Generalized muscular hyperalgesia I chronic whiplash syndrome. Pain 83:229–234
Kaergaard A, Andersen JH (2000) Musculoskeletal disorders of the neck and shoulders in female sewing machine operators: prevalence, incidence, and prognosis. Occup Environ Med 57:528–534
Kaish RA, Kaplan RF, Taylor E et al. (2001) Evaluation of study patients with Lyme disease, 10–20 year follow-up. J Infect Dis 1832:453–460
Kamakeri Y, Natvig B, Ihlebaek CM et al. (2008) Localized or widespread musculoskeletal pain: does it matter? Pain 138:41–46
Kaplan RF, Trevino RP, Johnson GM et al. (2003) Cognitive function in post-treatment-Lyme disease: do additional antibiotics help? Neurology 60:1916–1922
Kellgren JH (1938a) Observations on referred pain arising from muscle. Clin Sci 3:175–190
Kellgren JH (1938b) A preliminary account of referred pains arising from muscle. Br Med J 1:325–327
Kellgren JH (1949) Deep pain sensibility. Lancet 1:943–949
Klempner MS (2002) Controlled trials of antibiotic treatment in patients with post-treatment chronic Lyme disease. Vector Borne Zoonotic Dis 2:255–263
Krupp LB, Hyman LG, Grimson R et al. (2003) Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology 60:1923–1930
Kuan TS, Chen JT, Chen SM et al. (2002) Effect of botulinum toxin on endplate noise in myofascial trigger spots of rabbit skeletal muscle. Am J Phys Med Rehabil 81:512–520
Kuan LC, Li YT, Chen FM et al. (2006) Efficacy of treating abdominal wall pain by local injection. Taiwanese J Obstet Gynecol 45:239–243
Kuan TS, Hong CZ, Chen JT et al. (2007a) The spinal cord connections of the myofascial trigger spots. Eur J Pain 11:624–634
Kuan TS, Hsieh YL, Chen SM et al. (2007b) The myofascial trigger point region: correlation between the degree of irritability and the prevalence of endplate noise. Am J Phys Med Rehabil 86:183–189
Lambertz D, Hoheisel U, Mense S (2008) Influence of a chronic myositis on rat spinal field potentials evoked by TTX-resistant unmyelinated skin and muscle afferents. Eur J Pain 12:686–695
Lange U, Boss B, Teichmann T et al. (1999) Thyroid disorders in female patients with ankylosing spondylitis. Eur J Med Res 4:46–74
Lee SH, Chen CC, Lee CS et al. (2008) Effects of needle electrical intramuscular stimulation on shoulder and cervical myofascial pain syndrome and microcirculation. J Chin Med Assoc 71:200–206
Leedman PJ, Stein AR, Chin WW et al. (1996) Thyroid hormone modulates the interaction between iron regulatory proteins and the ferritin mRNA iron responsive element. J Biol Chem 271:12017–12023
Li LT, Ge HY, Yue SW et al. (2009) Nociceptive and non-nociceptive hypersensitivity at latent myofascial trigger points. Clin J Pain 25:132–137
Lowe JC (1997) Thyroid status of 38 fibromyalgia patients: implications for the etiology of fibromyalgia. Clin Bull Myo Therapy 2:47–64
Lucas KR, Polus BI, Rich PS (2004) Latent myofascial trigger points: their effect on muscle activation and movement efficiency. J Bodyw Mov Ther 8:160–166
Lucas KR, Rich PA, Polus BI (2007) Do latent trigger points affect muscle activation patterns? J Musculoskel Pain 15(Suppl 13):30
Lucas M, Macaskill P, Irwig L et al. (2009) Reliability of physical examination for diagnosis of myofascial trigger points. Clin J Pain 25:80–89
Madeleine P, Leclerc F, Arendt-Nielsen L et al. (2006) Clin Neurophysiol 117:2436–2445
Martin JV, Padron JM, Newman MA et al. (2004) Inhibition of the activity of the native gamma-aminobutyric acid A receptor by metabolites of thyroid hormone: correlation with molecular modeling. Brain Res 1004:98–102

McPartland JM, Simons DG (2006) Myofascial trigger points: translating molecular theory into manual therapy. J Man Manip Ther 14(4):232–239
Mense S (1993) Nociception from skeletal muscle in relation to clinical muscle pain. Pain 54:241–289
Mense S (2003) The pathogenesis of muscle pain. Curr Pain Headache Rep 7:419–425
Mense S (2009) Algesic agents exciting muscle nociceptors. Exp Brain Research 196:89–100
Mense S, Gerwin RD (eds) (2010) Muscle pain: understanding the mechanisms. Springer, Heidelberg
Mense S, Hoheisel U (2008) Mechanisms of central nervous hyperexcitability die to activation of muscle nociceptors. In: Graven-Nielsen T, Arendt-Nielsen L, Mense S (eds) Fundamentals of musculoskeletal pain. IASP, Seattle
Mense S, Simons DG, Hoheisel U et al. (2003) Lesions of rat skeletal muscle after local block of acetylcholinesterase and neuromuscular stimulation. J Appl Physiol 94:2494–2501
Michalaki M, Vagenakis AG, Maki M et al. (2001) Dissociation of the early decline in serum T(3) concentration and serum IL-6 rise and TNF-alpha in nonthyroidal illness syndrome induced by abdominal surgery. J Clin Endocrinol Met 86:4198–4205
Mills KR, Edward RH (1983) Investigative strategies for muscle pain. J Neurol Sci 58:73–78
Mithal A, Wahl DA, Bonjour JP et al. (2009) Global vitamin D status and determinants of hypovitaminosis D. Osteoporosis Int 20(11):1807–1820
Mitnick MA, Grey A, Masiukiewicz U et al. (2001) Parathyroid hormone induces hepatic production of bioactive interleukin-6 and its soluble receptor. Am J Physiol Endocrinol Metab 280:E405–E412
Mizumura K, Taguchi T (2008) Facilitated response of muscle thin-fiber receptors in mechanical hyperalgesia after exercise. In: Graven-Nielsen T, Arendt-Nielsen L, Mense S (eds) Fundamentals of musculoskeletal pain. IASP, Seattle
Moldofsky H (2008) The significance of the sleeping–waking brain for the understanding of widespread musculoskeletal pain and fatigue in fibromyalgia syndrome and allied syndromes. Joint Bone Spine 75:397–402
Molliver DC, Immke DC, Fierro L et al. (2005) ASIC3, an acid-sensing ion channel, is expressed in metaboreceptive sensory neurons. Mol Pain 1:35
Müller W, Stratz T (2004) Local treatment of tendinopathies and myofascial pain syndromes with the 5-HT3 receptor anatagonist tropisetron. Scand J Rheumatol 119 (Suppl):44–48
Müller W, Fiebich BL, Stratz T (2006) New treatment options using 5-HT3 receptor antagonists in rheumatic diseases. Curr Top Med Chem 6:2035–2042
Myburgh C, Larsen AH, Hartvigsen J (2008) A systematic, critical review of manual palpation for identifying myofascial trigger points: evidence and clinical significance. Arch Phys Med Rehabil 89:1169–1176
Nadelman RB, Nowakowski J, Forseter G et al. (1996) The clinical spectrum of early Lyme borreliosis in patients with culture-confirmed erythema migrans. Am J Med 100:502–508
Nagabukuro H, Berkley K (2007) Influence of endometriosis on visceromotor and cardiovascular responses induced by vaginal distention in the rat. Pain 132(Suppl 1):S96–S103
Nazareno J, Ponich T, Gregor J (2005) Long-term follow-up of trigger point injections for abdominal wall pain. Can J Gastroenterol 19:561–565
Newham DJ, McPhail G, Mills KR et al. (1983) Ultrastructural changes after concentric and eccentric contractions of human muscle. J Neurol Sci 61:109–122
Niddam DM, Chan RC, Lee SH et al. (2007) Central modulation of pain evoked from myofascial trigger point. Clin J Pain 23:440–448
Niddam DM, Chan RC, Lee CH et al. (2008) Central representation of hyperalgesia from myofascial trigger point. Neuroimage 39:1299–1306
Nijs J (2005) Generalized joint hypermobility: an issue in fibromyalgia and chronic fatigue syndrome. J Bodyw Mov Ther 9:310–317
Nocton JJ, Dressler F, Rutledge BJ et al. (1994) Detection of Borrelia burgdorferi DNA by polymerase chain reaction in synovial fluid in Lyme arthritis. N Eng J Med 330:229–234

Ofluoglu D, Gunduz OH, Kul-Panza E et al. (2006) Hypermobility in women with fibromyalgia syndrome. Clin Rheumatol 25:291–293
Okamoto K, Imbe H, Morikawa Y et al. (2002) 5-HT2A receptor subtype in the peripheral branch of sensory fibers is involved in the potentiation of inflammatory pain in rats. Pain 99:133–143
Pamuk ON, Cakir N (2007) The frequency of thyroid antibodies in fibromyalgia patients and their relationship with symptoms. Clin Rheumatol 26:55–59
Partanen J (1999) End plate spikes in the human electromyogram: revision of the fusimotor theory. J Physiol 93:155–166
Pavia CS (2003) Current and novel therapies for Lyme disease. Expert Opin Investig Drugs 12:1003–1016
Plotnikoff GA, Quigley JM (2003) Prevalence of severe hypovitaminosis D in patients with persistent, non-specific musculoskeletal pain. Mayo Clinic Proc 78:1463–1470
Pogrel MA, McNeill C, Kim JM (1996) The assessment of trapezius muscle symptoms of patients with temporomandibular disorders by use of liquid crystal thermography. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 82:145–151
Pointon JJ, Francis MJ, Smith R (1979) Effect of vitamin D deficiency on sarcoplasmic reticulum function and troponin C concentration of rabbit skeletal muscle. Clin Sci (Lond) 57:257–263
Punzi L, Betterie C (2004) Chronic autoimmune thyroiditis and rheumatic manifestations. Joint Bone Spine 71:275–283
Qerama E, Fuglsang-Frederiksen A, Kasch H et al. (2004) Evoked pain in the motor endplate region of the brachial biceps muscle: an experimental study. Muscle Nerve 29:394–400
Qerama E, Fuglsang-Frederiksen A, Kasch H et al. (2005) Effects of evoked pain on the electromyogram and compound muscle action potential of the brachial biceps muscle. Muscle Nerve 31:25–33
Radhakrishna M, Burnham R (2001) Infrared skin temperature measurement cannot be used to detect myofascial tender spots. Arch Phys Med Rehabil 82:902–905
Rashiq S, Galer BS (1999) Proximal myofascial dysfunction in complex regional pain syndrome: a retrospective prevalence study. Clin J Pain 15:151–153
Rickard LD (2006) The effectiveness of non-invasive treatments for active myofascial trigger point pain: a systematic review of the literature. Int J Osteopathic Med 9:120–136
Rollman G, Lautenbacher S (2001) Sex differences in musculoskeletal pain. Clin J Pain 17:20–24
Rosendal L, Larsson B, Kristiansen J et al. (2004) Increase in muscle nociceptive substances and anaerobic metabolism in patients with trapezius myalgia. Pain 112:324–334
Sacheti A, Szemere J, Bernstein B et al. (1997) Chronic pain is a manifestation of the Ehlers–Danlos syndrome. J Pain Symptom Manage 14:88–97
Santillan G, Katz S, Vasquez G et al. (2004) TrPC3-like protein and vitamin D receptor mediate 1 alpha, 25(OH)2D3-induced SOC influx in muscle cells. Int J Biochem Cell Biol 36 (10):1910–1918
Santiná PV, de Alenacar Júnior FGP (2009) Myofascial pain syndrome as a contributing factor in patients with chronic headaches. J Musculoskel Pain 17(1):15–25
Sato Y, Inose M, Higuchi F et al. (2002) Changes in the supporting muscles of the fractured hip in elderly women. Bone 30:325–330
Sciotti VM, Mittak VL, DiCarco L et al. (2001) Clinical precision of myofascial trigger point location in the trapezius muscle. Pain 93:259–266
Scott NA, Guo B, Barton PM et al. (2009) Trigger point injections for chronic non-malignant musculoskeletal pain: a systematic review. Pain Med 10:54–69
Seaverson EL, Buell JS, Fleming DJ et al. (2007) Poor iron status is more prevalent in Hispanic than in non-Hispanic white older adults in Massachusetts. J Nutr 137:414–420
Serratrice G, Gastaut JL, Schiano A et al. (1980) Diffuse myalgias. A series of 210 cases. Sem Hop Paris 56:1241–1244 [French]
Shah JP, Gilliams EA (2008) Uncovering the biochemical milieu of myofascial trigger points using in vivo microdialysis: an application of muscle pain concepts to myofascial pain syndrome. J Bodyw Mov Ther 12:371–384

Shah JP, Phillips TM, Danoff JV et al. (2005) An in vitro mircroanalytical technique for measuring the local biochemical milieu of human skeletal muscle. J Appl Physiol 99:1977–1984
Shah J, Danoff JV, Desai MJ et al. (2008) Biochemicals associated with pain and inflammation are elevated in sites near to and remote from active myofascial trigger points. Arch Phys Med Rehabil 89(1):16–23
Shultz SP, Driban JB, Swanik CB (2007) The evaluation of electrodermal properties in the identification of myofascial trigger points. Arch Phys Med Rehabil 88:780–784
Sikdar S, Shah JP, Gilliams E et al. (2008) Assessment of myofascial trigger points (MTrPs): a new application of ultrasound imaging and vibration sonoelastography. Proceedings of the 30th Annual International IEEE EMBS Conference, Vancouver, British Columbia, Canada, 5585–5588
Simons DG (2001) Do endplate noise and spikes arise from normal motor endplates? Am J Phys Med Rehabil 80:134–140
Simons DG, Stolov WC (1976) Microscopic features and transient contraction of palpable bands in canine muscle. Am J Phys Med 55:65–88
Simons DG, Hong CZ, Simons LS (1995) Prevalence of spontaneous electrical activity at trigger points and at control sites in rabbit skeletal muscle. J Musculoskel Pain 3(1):35–48
Simons DG, Travell JG, Simons LS (1999) Myofascial pain and dysfunction: The trigger point manual, vol. 1, 2nd edn. Williams & Wilkins, Baltimore
Simons DG, Hong C-Z, Simons LS (2002) Endplate potentials are common to midfiber myofascial trigger points. Am J Phys Med Rehabil 81:212–222
Simpson RU, Thomas GA, Arnold AJ (1985) Identification of 1, 25-dihydroxy vitamin D3 receptors and activities in muscle. J Biol Chem 260:8882–8891
Skootsky SA, Jaeger B, Oye RK (1989) Prevalence of myofascial pain in general internal medicine practice. West J Med 151:157–160
Skyba DA, King EW, Sluka KA (2002) Effects of NMDA and non-NMDA ionotropic glutamate receptor antagonists on the development and maintenance of hyperalgesia induced by repeated intramuscular injection of acidic saline. Pain 98:69–78
Sluka K (2002) Stimulation of deep somatic tissue with capsaicin produces long-lasting mechanical allodynia and a heat hypoalgesia that depends on early activation of the cAMP pathway. J Neurosci 22:5687–5693
Sluka K, Kalra A, Moore SA (2001) Unilateral intramuscular injections of acidic saline produce a bilateral, long-lasting hyperalgesia. Muscle Nerve 24:37–46
Sluka KA, Price MP, Breese NM et al. (2003) Chronic hyperalgesia induced by repeated acid injections in muscle is abolished by the loss of ASIC3, but not by ASIC1. Pain 106:229–239
Sorenson OH, Lund B, Saltin B et al. (1979) Myopathy in bone loss of ageing: improvement by treatment with 1 alpha-hydoxycholecalciferol and calcium. Clin Sci (Lond) 56(2):157–161
Sorvillo F, Massiotti G, Carbone A et al. (2003) Increased serum reverse triidothyronine levels at diagnosis of hepatocellular carcinoma in patients with compensated HCV-related liver cirrhosis. Clin Endocrinol 56:207–212
Srbely JZ, Dickey JP (2007) Randomized controlled study of the antinociceptive effect of ultrasound on trigger point sensitivity: novel applications in myofascial therapy. Clin Rehabil 21:411–417
Srbely JZ, Dickey JP, Lowerison M et al. (2008) Stimulation of myofascial trigger points with ultrasound induces segmental antinociceptive effects: a randomized controlled study. Pain 139:260–266
Srinivasan R, Greenbaum DS (2002) Chronic abdominal wall pain: a frequently overlooked problem. Practical approach to diagnosis and management. Am J Gastroenterol 97:824–830
Srivivasan AK, Kaye JD, Moldwin R (2007) Myofascial dysfunction associated with chronic pelvic floor pain: management strategies. Curr Pain Headache Rep 11:359–364
Staffel K, del Mayoral del Moral, Lacomba MT et al. (2007) Factors that influence the reliability of clinical assessment for the classification of the myofascial pain syndrome. J Musculoskel Pain 15(Suppl 13):36

Steere AC (2002) A 58-year-old man with a diagnosis of chronic Lyme disease (Clinical Crossroads). JAMA 288:1002–1010
Stratz T, Müller W (2004) Treatment of chronic low back pain with tropisetron. Scand J Rheumatol Suppl 119:76–78
Sun RQ, Tu YJ, Lawand NB et al. (2004) Calcitonin gene-related peptide receptor activation produces PKA and PKC-dependent mechanical hyperalgesia and central sensitization. J Neurophysiol 92:2859–2866
Sung D, Dong X, Ernberg M et al. (2008) Serotonin (5-HT) excites rat masticatory muscle afferent fibers through activation of peripheral 5-HT receptors. Pain 143:41–50
Taguchi T, Hoheisel U, Mense S (2008) Dorsal horn neurons having input from low back structures in rats. Pain 138:119–129
Tang B, Ji Y, Traub RJ (2008) Estrogen alters spinal NMDA receptor activity via a PKA signaling pathway in a visceral pain model in the rat. Pain 137:540–549
Tangpricha V, Pearce EN, Chen TC et al. (2002) Vitamin D insufficiency among free-living healthy young adults. Am J Med 112:659–662
Tienboon P, Unachak K (2003) Iron deficiency anaemia in childhood and thyroid function. Asia Pac J Clin Nutr 12:198–202
Tokinaga K, Oeda T, Suzuki Y et al. (2006) HMG-CoA reductase inhibitors (statins) might cause high elevations of creatinine phosphokinase (CK) in patients with unnoticed hypothyroidism. Endocr J 53:401–405
Tough EA, White AR, Richards S et al. (2007) Variability of criteria used to diagnosis myofascial trigger point pain syndrome — evidence from a review of the literature. Clin J Pain 23:278–286
Tough EA, White AR, Cummings TM et al. (2008) Acupuncture and dry needling in the management of myofascial trigger point pain: a systematic review and meta-analysis of randomized controlled trials. Eur J Pain 13:3–10
Travell J (1954) Introductory comments. In Ragan C (ed), Connective Tissues, Transactions of the Fifth Conference, Josiah Macy, Jr. Foundation, New York, pp 12–22
Travell JG (1990) Chronic myofascial pain syndromes: mysteries of the history. In: Friction JR, Awad E (eds) Advances in pain research and therapy, vol 17. Raven, New York
Travell JG, Rinzler SH (1952) The myofascial genesis of pain. Postgrad Med 11:425–434
Travell JG, Simons DG (1983) Myofascial pain and dysfunction: the trigger point manual. Williams & Wilkins, Baltimore
Travell JG, Simons DG (1992) Myofascial pain and dysfunction: the trigger point manual, vol 2. Williams & Wilkins, Baltimore
Treaster DE, Burr D (2004) Gender differences in prevalence of upper extremity musculoskeletal disorders. Ergonomics 15:495–526
Treaster D, Marras WS, Burr D et al. (2006) Myofascial trigger point development from visual and postural stressors during computer work. J Electromyogr Kinesiol 16:115–124
Tsigos C, Chrousos GP (2002) Hypothalamic pituitary adrenal axis, neuroendocrine factors and stress. J Psychosom Res 4:865–871
Van den Berghe C, de Zegher F, Baxter RC et al. (1998) Neuroendocrinology of prolonged critical illness: effects of exogenous thyrotropin-releasing hormone and it combination with growth hormone secretagogues. J Clin Endocrinol Metab 83:309–319
Verkhouvsky MI, Morgan JE, Puustinen A et al. (1996) The "ferrous-oxy" heme intermediate in the reaction of dioxygen with fully reduced cytochromes aa3 and bo3. Biochemistry 35:16241–16246
Von Restorff C, Bischoff-Ferrari HA, Theiler R (2009). High dose oral vitamin D3 supplementation in rheumatology patients with severe vitamin D3 deficiency. Bone 45(4):747–749
Wang J, O'Reilly Venkataraman R, Mysliwiec V et al. (2009) Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: a randomized, double-blind, placebo-controlled study. Sleep Med 10(9):973–975
Wassner SJ, Li JB, Sperduto A et al. (1983) Vitamin D deficiency, hypocalcemia, and increased skeletal muscle degradation in rats. J Clin Invest 72:102–112

Weinstein A, Britckov M (2002) Lyme Arthritis and post-Lyme disease syndrome. Curr Opin Rheumatol 14:383–387

Weijenborg PT, Greeven P, Dekker TW, Peters AA, Ter Kuile MM (2007) Clinical course of chronic pelvic pain in women. Pain 132 (Suppl 1):117–123

Witzke O, Winterhagen T, Saller B et al. (2001) Transient stimulatory effects on pituitary-thyroid axis in patients treated with interleukin-2. Thyroid 11:665–670

Wolfe F, Smythe HA, Yunus MB et al. (1990) The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. Arthritis Rheum 33:160–172

Yavuz O, Yavuz T, Kahraman C et al. (2004) The relationship between iron status and thyroid hormones in adolescents living in an iodine deficient area. J Pediatr Endocrinol Metab 17:1443–1449