A review of myofascial pain and fibromyalgia – factors that promote their persistence

Robert D Gerwin

Abstract

Chronic muscle pain (myalgia) is a common problem throughout the world. Seemingly simple, it is actually a difficult problem for the clinician interested in determining the aetiology of the pain, as well as in managing the pain. The two common muscle pain conditions are fibromyalgia and myofascial pain syndrome. Fibromyalgia is a chronic, widespread muscle tenderness syndrome, associated with central sensitisation. It is often accompanied by chronic sleep disturbance and fatigue, visceral pain syndromes like irritable bowel syndrome and interstitial cystitis. Myofascial pain syndrome is an overuse or muscle stress syndrome characterised by the presence of trigger points in muscle. The problem these syndromes pose lies not in making the diagnosis of muscle pain. Rather, it is the need to identify the underlying cause(s) of persistent or chronic muscle pain in order to develop a specific treatment plan. Chronic myalgia may not improve until the underlying precipitating or perpetuating factor(s) are themselves managed. Precipitating or perpetuating causes of chronic myalgia include structural or mechanical causes like scoliosis, localised joint hypomobility, or generalised or local joint laxity; and metabolic factors like depleted tissue iron stores, hypothyroidism or Vitamin D deficiency. Sometimes, correction of an underlying cause of myalgia is all that is needed to resolve the condition.

Keywords

Myalgia, hypothyroidism, trigger points, referred pain, fibromyalgia, myofascial pain syndrome.

Robert D Gerwin
neurologist
Bethesda, Maryland
USA

gerwin@painpoints.com

This is a really good article, I have indicated the labs Dr. Gerwin uses to help c FMS, CMPS pts.

Dr. Gerwin was in practice c Dr. Travell + he teaches the DN'ng

Please share c others if you find it helpful, I know it is long But is a quick read.

Introduction to fibromyalgia and myofascial pain

Myalgia is muscle pain or pain of muscular origin, irrespective of cause. There are two major types of non-inflammatory myalgia that are commonly diagnosed. One is fibromyalgia (FMS). It is a syndrome in which there is chronic, widespread muscle tenderness as a result of central sensitisation. FMS is denoted as primary when there is no co-existent disease that causes widespread muscle pain. FMS is considered secondary when myalgia is co-morbid with other disorders. Myofascial pain syndrome (MPS), the other common muscle pain syndrome, is associated with discrete taut bands of hardened muscle that contain regions of exquisite muscle tenderness. It, too, may be a central hypersensitivity syndrome, but little research has been done on this point in MPS. A striking property of MPS painful regions is that they generate referred pain that is felt in a different, usually distal, site. The site of referred pain perception can be in the same limb, in the same region, in the body wall, or in a visceral organ. Referred pain tends to be segmental, so that referred pain patterns are usually located in sites innervated by adjacent or nearby spinal cord segments. Hence, trigger points in the posterior shoulder muscles like the supraspinatus and infraspinatus muscles that are innervated by C5 refer pain to the shoulder (C4-5 dermatomes) and the arm and hand (C5-6-7-8 dermatomes). Likewise, upper cervical spine muscle trigger points, that have an input into the descending (caudal) trigeminal nucleus, refer pain to the head, because the meninges and the face are innervated by the trigeminal nerve.

Myalgia can be a primary chronic pain state in which there are no diagnostic laboratory abnormalities that are specific for FMS or MPS. Myalgia that lasts for three months or longer is considered chronic. It can be a disabling generalised pain that is often associated with disturbed rest and debilitating fatigue. Treatment success may be limited. Treatment of co-morbid myalgia can also

be difficult, especially if a treatable cause of a co-morbid illness cannot be found.

FMS and MPS both give rise to muscle tenderness, but beyond that common phenomenon they differ and form two distinct entities. FMS is a syndrome (not a disease) of central sensitisation and augmentation that results in widespread musculoskeletal tenderness and pain. MPS is also a syndrome. It is the result of a local muscle metabolic stress that is thought to produce an energy crisis that does not support a specific muscle action. It may develop after one maximal contraction or excessive eccentric contraction in an untrained muscle.[1] It is associated with a discrete linear band-like hardness or tautness (trigger points) within one or more muscles, leading to the release of nociceptive substances such as substance P, potassium, and histamine that activate peripheral nociceptive receptors and dorsal horn nociceptive neurons. Biochemical changes at the heart of the trigger zone (elevated levels of calcitonin gene-related peptide, of substance P, norepinephrine, and tumour necrosis factor-1α, and of interleukin 1 and 6, and a low pH of 3.0 to 4.0) have been identified by Shah et al.[2] A region of the taut band is exquisitely tender and can refer pain to another, usually distal, region. Sleep disturbance in addition to pain will more likely result in the diagnosis of FMS. Exercise intolerance can be seen with either FMS or MPS. Many cases of FMS are in fact cases of MPS that have been misdiagnosed as a result of poor muscle palpation techniques that miss the presence of taut bands and referred pain. Nevertheless, the comments regarding underlying, etiological or co-morbid disorders are applicable to both syndromes. There is always the possibility that muscle pain associated with exercise intolerance and fatigue can be due to a problem that is neither FMS or MPS, such as that seen with a mutation in the cytochrome b gene of mitochondrial DNA (mtDNA),[3] Lyme Disease, vitamin D deficiency, perhaps myoadenylate deaminase deficiency, or hypothyroidism. Thus, the diagnosis of FMS or MPS based on the presence of muscle pain, fatigue, and exercise intolerance, and the physical findings of tenderness or of myofascial trigger points, is not sufficient to give primary consideration solely to FMS or MPS.

Table 1 **The tender points used to diagnose fibromyalgia**

1	suboccipital muscle
2	anterior cervical at C6
3	upper trapezius
4	supraspinatus
5	parasternal at the 2nd intercostal space
6	lateral epicondyle
7	upper outer quadrant of the gluteal muscles
8	greater trochanter
9	medial knee above the joint line (medial fat pad or vastus medialis muscle)

Each point is examined bilaterally for a total of 18 points.

Fibromyalgia

Characteristics

FMS is a chronic, widespread myalgia that by definition involves the body above and below the waist, and to the right and left sides of the midline, such that three or four quarters of the body are involved. Chronic and widespread pain of muscle origin are reflected in the criteria for diagnosis published by the American College of Rheumatology (ACR).[4] Using the ACR criteria, 3.5% of women and 0.5% of men in the United States have been estimated to have FMS. The ACR criteria, intended to provide a uniform definition of fibromyalgia for research studies, require that: 1) symptoms have been present for at least three months; and 2) 11 sites of a specified 18 sites be tender (Table 1). Diagnosis of FMS in clinical practice was never intended to be as strict as that required for research purposes. Chronic and widespread muscular pain are still required to make the diagnosis, but the extent of muscle tenderness may vary over time, and there may be far fewer than 11 tender sites found on examination at any given time. Chronic symptoms including widespread tenderness distinguish FMS from other musculoskeletal pain syndromes with a specificity of 81% and a sensitivity of 88%.[4] However, they do not distinguish FMS from chronic, widespread MPS or any other chronic condition where there is widespread muscle tenderness, since tenderness is the sole significant physical finding specified in the ACR criteria. In fact, MPS is the most common condition that must be considered in the differential diagnosis.[5]

Any condition associated with myofascial trigger points will produce tenderness to palpation. Such conditions include nutritional deficiency states such as iron insufficiency, vitamin B12 deficiency, hormonal disorders eg hypothyroidism, and trauma eg cervical strain injury ('whiplash'). Consequently, the physical examination performed for the evaluation of myalgia must include palpation for the taut bands of myofascial trigger points (see below), including an attempt to elicit referred pain, as well as for the tender points of FMS. A comprehensive medical evaluation is also indicated in order to identify conditions in which diffuse myalgia occurs secondarily. A localised or regional muscular pain syndrome such as that associated with whiplash is not FMS when there is no widespread muscle pain that occurs above and below the waist. Even when there is widespread pain, it may be due to MPS, and not to FMS.

The acceptance of the ACR criteria fostered a virtual explosion in the publication of research studies on the nature of fibromyalgia, even though the diagnostic criteria were criticised as invalid and based on circular reasoning. Nevertheless, despite the criticism, the criteria serve a useful purpose as similarly established criteria do in other chronic or recurring pain states that lack objective markers, such as non-specific low back pain and migraine headache without aura. The clinical diagnosis of FMS continues to be based on the history and physical examination. Laboratory tests and imaging procedures are not useful for making a positive diagnosis, but are required to evaluate the patient for co-morbid conditions or to identify other reasons for the chronic pain.

Associated symptoms

FMS is above all else a chronic muscular pain syndrome,[6] but it is associated with a number of other symptoms that include sleep disturbance and fatigue, headache, morning stiffness, irritable bowel syndrome (IBS), interstitial cystitis (IC), dyspareunia, and mood disturbance. Some of these symptoms are manifestations of referred muscle pain from myofascial trigger points (headache, dyspareunia, morning stiffness), and others, like IBS and IC are viscerosomatic pain syndromes,[7] that occur more frequently in persons with FMS (up to 70% in FMS patients). The viscerosomatic syndromes are by no means unique to FMS, and are usually associated with pelvic floor MPS syndromes. Depression may occur in as many as 30% of FMS patients, but is also said to be no more common in FMS than in the general population.

Pathophysiology

Fibromyalgia has been extensively studied to try to identify an underlying physiological or biochemical basis to explain the fatigue and the muscle tenderness. Evidence has accumulated that tenderness in FMS is related to central sensitisation with amplification of nociception, resulting in a broad array of stimuli perceived as being more painful among FMS patients than they are in control populations.[8-11] This is a fundamental abnormality that is very likely related to the cause of fibromyalgia. Increased substance P in cerebral spinal fluid may be relevant to the generalised hypersensitivity (which includes 'hypervigilance') seen in FMS. Sleep disturbance, with lack of sustained stage three and four sleep and intrusion of alpha activity into delta-wave sleep, has been reported in FMS, and patients complain of non-restorative, non-refreshing sleep. Alterations in cardiovascular autonomic nervous system function lead to orthostatic hypotension, or neurally-mediated orthostatic tachycardia,[12] further aggravating fatigue and impaired ability to function. Neuroendocrine abnormalities in the hypothalamic-pituitary-adrenal system, and growth hormone deficiency, are hormonal deficiency states that may tie together the symptoms of fatigue, pain and sleep and mood disturbances.[13] Growth hormone is secreted during sleep; the deficiency of serotonin in FMS leads to sleep disturbances and possibly to the decrease in growth hormone secretion. Interleukin-8 levels are increased in FMS patients and related to pain intensity, suggesting a role for cytokines in the aetiology of FMS.

The long-term prognosis of FMS is more favourable than initially thought. Symptoms may persist for years, but patients either learn to cope with the chronic pain, or the pain does not progress. A substantial percentage of FMS patients reported some lessening of pain over the years, even though they were still symptomatic. Functioning improves over the years, particularly in the older population (55 to 64 years old), possibly because of more effective coping skills. Symptoms decrease with age, and older patients have less pain, depression, illness impact, and better sleep.[14]

Treatment

Treatment of fibromyalgia has included a wide variety of pharmacological, nutritional, hormonal, behavioural, cognitive, exercise and physical modalities. Extensive experience in the use of antidepressants in the treatment of FMS has accumulated over the years. Amitriptyline potentiates the analgesic effect of opioids, and it, as well as other tricyclic antidepressants and the new antidepressants, venlafaxine and duloxetine, inhibit the re-uptake of serotonin and norepinephrine at neuronal terminals. Amitriptyline at 25-50mg at bedtime produces initial improvement that has not been shown to be sustained more than six months.[15] The new serotonin and norepinephrine reuptake inhibitor duloxetine, and the new anticonvulsant pregabalin have both been shown to be effective in reducing the symptoms of FMS. Antidepressant treatment improves sleep, fatigue, pain and wellbeing, but does not change tender point counts. A problem with the clinical trials of tricyclic antidepressant therapy is that they are of short duration. Only one study lasted 6.5 months, and it showed no greater effectiveness for amitriptyline than for placebo.

A modest benefit is achieved with growth hormone (GH) replacement in the subset of about one in three FMS patients who have a demonstrated deficiency of GH or insulin-growth-factor-1. The treatment is expensive, and is of benefit only as long as the replacement is given. Thyroid hormone replacement is likewise beneficial in those patients who have demonstrated hypothyroidism, but there are no data that suggest that hypothyroidism is more common in FMS than in the general population.

Graded, progressive exercise programmes provide both short and long-term improvement in FMS. Cognitive therapy is effective when combined with exercise. Supplements such as guaiphenesin and dehydroepiandrosterone sulphate (DHEAS), magnesium, and S-adenosylmethionine (SAMe) are commonly used, but there are few data to show that they are effective in the management of FMS.[16] A committee of the American Pain Society recently reviewed the evidence for effectiveness of currently available treatment recommended for fibromyalgia.[17] They found strong evidence to support the use of low dose tricyclic antidepressants and cylcobenzaprine, cardiovascular exercise, cognitive behavioural therapy, and patient education. There was moderate evidence for the use of tramadol, selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, and certain anticonvulsant drugs. Moderate evidence also exists for the efficacy of strength training, acupuncture, hypnotherapy, biofeedback, massage and warm water baths. Many commonly used treatments were found not to have been well evaluated.

Myofascial Pain Syndrome

Characteristics

MPS is a muscular pain syndrome that arises from a primary dysfunction in muscle and yet is associated with central sensitisation and a segmental spread within the spinal cord to give rise to the phenomenon of referred pain, or pain that is felt at a distance.[18] The clinical picture of MPS is one of musculoskeletal pain, limited mobility, weakness and referred pain.[19] There may be clumsiness and in-coordination as well. The specifics of the MPS in a given individual are dependent on which muscles are involved. Involvement of the muscles of the head, neck and shoulders gives rise to headache and neck and shoulder pain. Involvement of the pelvic floor muscles causes pain referred to the viscera (bowel, bladder and genitourinary tract organs). Hamstring muscle involvement can impair sitting because of pain felt at the ischial tuberosity, and can also cause pain that is felt behind the knee. Pain can be felt at the site of the muscle dysfunction, called the Myofascial Trigger Point (MTrP), and also in the region of referred pain. For example, trigger points in the subscapularis muscle can cause both local shoulder pain and pain at the wrist.

The features of the trigger point itself comprise both a taut band and pain. This duality of the MTrP emphasises the two main characteristics of the MTrP: a motor or architectural abnormality and a painful sensory dysfunction. The motor abnormality is an abnormal hardness in the muscle that is felt on palpation of the muscle. One or several bands within the muscle are felt to be hard, stiff or taut. The usual description is that of a taut band. It is discrete within the muscle, and generally extends the full length of the muscle between tendons or tendinous bands (like the inscription bands in the rectus abdominis or hamstring muscles). The entire muscle is not hard or cramped, nor is it tender. The exquisite tenderness is present only over the taut band.

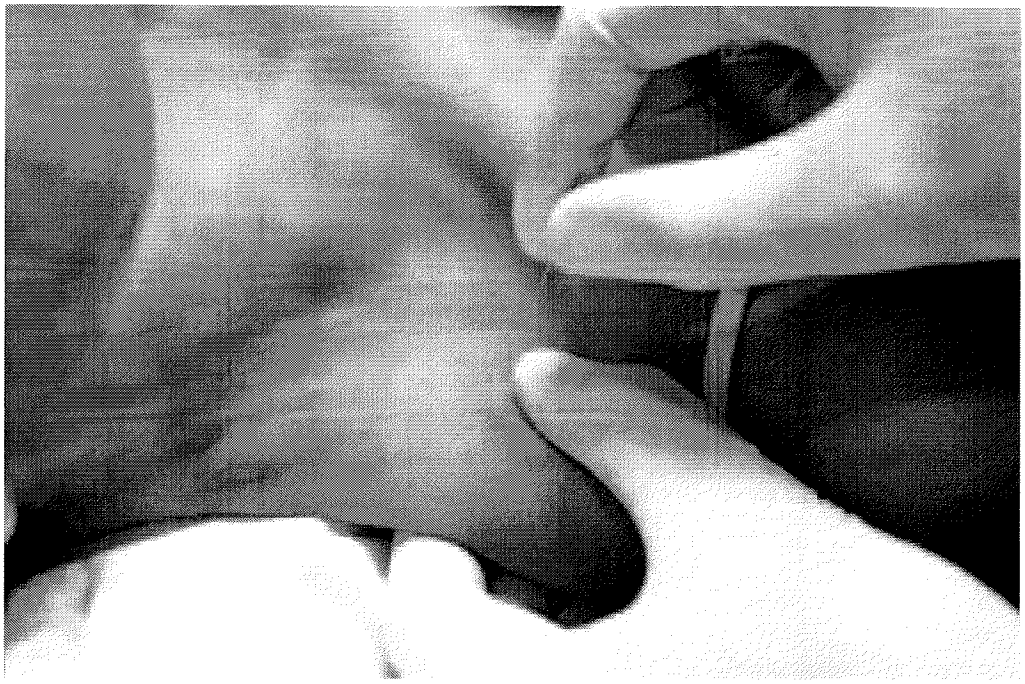

Figure 1 This image shows how a taut band in the upper trapezius fibres is palpated and fixed to allow safe dry needling of the trigger point with an acupuncture needle.

The taut band is the primary identifiable abnormality accessible to physical examination in the muscle, and may be present without tenderness. However, tenderness in MPS is not present without a taut band. The clinical diagnosis is made by physical examination (Table 2).

Identification of the trigger point by physical examination has good inter-rater reliability.[20] A characteristic electromyographic discharge termed spontaneous electrical activity (SEA) is associated with the taut band. The term SEA has been replaced by the more accurate term 'end plate noise'. Low amplitude (10-50μV) discharges are present in the taut band, whether painful or not. Intermittent high amplitude (up to 500μV) discharges are seen in painful trigger points. The electrical discharges have the characteristics of miniature end plate potentials except that they occur with a frequency that is 10-100 times that of normal end plate potential discharges. They are likely to occur as the result of an abnormally excessive, spontaneous release of acetylcholine from the synaptic terminal of the motor nerve fibre. This has not been proven, however. The taut band has the characteristic that when it is stimulated mechanically it contracts sharply. Mechanical stimulation, either by strumming the taut band or by needling it, results in a mechanical deformation of the band. A sharp contraction of the muscle in response to needling is seen on electromyographic recordings as a high amplitude (1-2mV) polyphasic discharge of up to 250 milliseconds duration. It is maximally elicited from the most tender region of the taut band, diminishes with increasing distance from that point, and is not elicited when recording from normal muscle as little as 10mm from the taut band. Endplate noise is reduced by as much as 22% by the infusion of phentolamine – an alpha 2 presynaptic blocker that inhibits adrenergic sympathetic activity.[21] Phentolamine causes an increase in the release of norepinephrine into the synapse by blocking the alpha 2 inhibitory action of endogenous norepinephrine. Beta adrenergic receptors can be stimulated by this action, as for example in the heart.

Table 2 **Essential diagnostic features of myofascial pain**

1	hardness or taut band in a muscle
2	tenderness in the hardened or taut band of muscle
3	reproduction of usual or spontaneous pain

Thus, the abnormal spontaneous electrical activity associated with the taut band is modulated by the sympathetic nervous system, most likely by activity of adrenoreceptors on the motor nerve terminal.

The sensory abnormality is that of muscle tenderness, felt as both local and referred pain. Experimental models of muscle pain demonstrate that central sensitisation occurs in response to noxious stimulation in the presence of a persistent irritating stimulus, such as an injection of bradykinin into the muscle. This results in lowering the threshold for pain and increasing the number and size of the receptive fields to which a single dorsal horn nociceptive neuron responds (Mense et al *Muscle Pain* p 84-98).[18] In the human, this is expressed as hypersensitivity or allodynia, manifest as tenderness, spontaneous pain, or referred pain. The relationship between the taut band and pain is explained by the integrated hypothesis of Simons (Mense et al *Muscle Pain* p 252-7).[18] In this hypothesis, an excess release of acetylcholine at the motor end-plate results in the creation of taut bands in the affected muscle that compress capillaries thereby decreasing local blood flow and causing ischemia. Ischemia limits the availability of oxygen and glucose, thereby creating an energy crisis in the working muscle. As a result, potassium, histamine, substance P and other excitatory substances that activate peripheral nerve nociceptive receptors are released, stimulating dorsal horn nociceptive neurons and causing pain.

Spread through functional units

Myofascial pain spreads through the involvement of functional muscle units, or muscles that work together either as agonists or antagonists. An MTrP restricts the range of motion related to a specific muscle, and weakens the muscle. Compensation for the impaired function of the muscle loads other muscles in the functional unit. For example, if the upper trapezius muscle is impaired because of myofascial trigger points, the levator scapulae muscle will be overloaded in controlling scapular motion, and the posterior cervical muscles like the semispinalis capitis will be overloaded in extending the neck. Myofascial pain can also spread through axial dysfunction. Trigger points in the psoas or quadratus lumborum muscles can produce a pelvic tilt that looks like a leg-length inequality, causing scoliosis. Shoulder tilt occurs to accommodate the spinal curvature, and to level the eyes with the horizon. The shoulder and neck muscles must level the head. Chronic muscle contraction to bring the spine back to the midline can produce trigger points and myofascial pain. Thus, a local or regional myofascial syndrome can spread through the body and become a widespread myofascial syndrome (Table 3).

Table 3 **Causes of persistent myalgia**

Category	Problem
Mechanical	Structural
	Postural
	Ergonomic
Medical	Infectious diseases
	Inflammatory disorders
	Immunological/allergic
	Nutritional disorders
	Hormonal disorders

Non-structural perpetuating factors

Medical factors that result in neurological functional impairment include vitamin B12, other vitamin insufficiency states, iron insufficiency, thyroid deficiency states, and chronic infections, such as Lyme disease, and recurrent Candida albicans infections in women.

Nutritional deficiencies

Vitamin B12 deficiency is a common problem that affects an increasing percentage of persons over the age of 65 because the synthesis of intrinsic factor decreases with age. As many as 15-20% of persons over the age of 65 are estimated to be deficient.[22,23] Moreover, the pathways of absorption and utilisation are complex and there are many mutations that can occur that reduce absorption or metabolic activity. Folic acid corrects the anaemia of B12 deficiency, but not the neuromuscular deficit. Thus, pernicious anaemia is a marker of B12 deficiency, but is not adequate alone because B12 deficiency exists in the absence of anaemia. The non-haematological manifestation of B12 deficiency is nerve dysfunction in the brain (cognitive impairment), the spinal cord (combined degeneration of the cord), and in the peripheral nerve (neuropathy). It is likely that the peripheral neuropathy is linked to the diffuse myalgia

that is sometimes seen in B12 deficiency and that improves with B12 replacement. If serum B12 concentration is below 300pg/ml, methylmalonic acid and homocysteine are good markers for metabolic abnormalities caused by B12 insufficiency. However, there may be metabolic abnormalities of B12 function even in the absence of elevations of methylmalonic acid or homocysteine.

Iron deficiency in muscle occurs when muscle ferritin is depleted. This occurs at serum ferritin levels of about 15ng/ml. The prevalence of iron deficiency in females age 12-49 is 9-16%. It is higher in African-Americans and Hispanics (19-22%). Iron is essential for the generation of energy through the cytochrome oxidase enzyme system. Iron deficiency causes fatigue, poor endurance and can cause muscle pain. Replacement is available both by the oral and intravenous route.

Iron deficiency has been generally defined as a level of iron that is associated with anaemia. Levels vary with age and sex, falling in adolescence with increased growth and, in girls, with the onset of menstrual blood loss. Iron stores rise again in adulthood, and again in post-menopausal women. This variation is important in assessing iron stores as a possible factor contributing to muscle pain, particularly in adolescent girls and in pre-menopausal women. Iron stores are assessed best by measuring serum ferritin. Anaemia is associated with ferritin levels below 10ng/ml.[24] However, iron loss as determined by low ferritin levels does not correlate directly with anaemia. The first stage of iron loss is associated with depletion of freely accessible iron stores in muscle, liver and bone marrow when the serum ferritin level is about 15ng/ml. The second stage of iron deficiency is erythrocyte microcytosis without anaemia. The third stage is anaemia, by which time iron bone marrow stores are undetectable. Symptoms such as chronic tiredness, unusual fatigue with exercise, and coldness begin with the first stage of iron loss. Optimum ferritin levels are unknown for normal muscle function, but Sun et al reported that in restless leg syndrome, another condition aggravated by iron deficiency or in some cases caused by it, serum ferritin levels below 50ng/ml were associated with a worsening of restless legs syndrome.[25] In this same condition, but in adolescents and children under the age of 18, the serum ferritin level was below 20ng/ml in 50% of cases, below 25ng/ml in 60% of cases, and below 50ng/ml in 83% of cases studied.[26] This suggests that not only are serum ferritin levels below 20-25ng/ml clinically significant in restless legs syndrome, but that levels below 50ng/ml are possibly clinically significant and likely to be suboptimal. One cannot make a direct relationship from these data to determine the optimal levels of ferritin in the development of muscle pain, but this gives some general guidance as to what might be considered minimally optimal and suboptimal levels of serum ferritin.

A deficiency of freely accessible iron in muscle creates an energy crisis in muscle by limiting an energy producing reaction. In this way, iron deficiency can be a factor in the development or maintenance of myofascial trigger points. Moreover, with respect to the role that iron plays in contributing to a sleep disorder through producing restless legs syndrome, there is a connection between iron deficiency, sleep deprivation and myalgia. Restless legs syndrome is associated with a sleep disturbance or sleep deprivation, with reduced levels of, or absence of, deep sleep. Thus, iron insufficiency associated with restless legs syndrome can be indirectly also associated with myalgia.

Vitamin D deficiency is associated with musculoskeletal pain, loss of type II muscle fibres, and proximal muscle atrophy.[27,28] Plotnikof and Quigley found that 89% of subjects with chronic musculoskeletal pain were deficient in Vitamin D.[29] The diagnosis was made by measuring 25-OH vitamin D. Values above 20ng/ml were considered normal. However, other studies suggest that levels below 34ng/ml represent vitamin D deficiency. Vitamin D deficiency is easily detected by measuring 25-OH vitamin D. The deficiency state is easily corrected, but it takes up to six months of replacement to reverse changes caused by deficiency states. People not exposed to the sun are at great risk, including those whose clothes leave little skin exposed to the sun, and those who spend little time out of doors.

Hormonal dysfunction

a) Hypothyroidism

Observations of patients with chronic myalgia suggest that hypothyroidism is causally linked to this condition. There is some evidence to support thyroid dysfunction in FMS, but little epidemiological evidence to confirm the clinical impression that thyroid

dysfunction is associated with chronic myofascial pain syndrome. However, the absence of such data may lie in flaws in the studies themselves.

Underactive thyroid function is a form of hypometabolism. It can occur as a result of insufficient production of T4, either because of insufficient secretion of thyroid releasing hormone (TRH) as a result of a lack of hypothalamic responsiveness, or because of thyroid disease itself, such as Hashimoto's thyroiditis. It also occurs because of impaired conversion of T4 to T3. Conversion of inactive to active thyroid hormone is the result of 5'-deiodination of T4 and occurs in the liver.[30] Peripheral suppression of thyroid hormone activity also occurs in 'non-thyroidal illness syndrome' (previously call the 'sick euthyroid syndrome'). Acute and chronic stress also affects the hypothalamic-pituitary-adrenal axis, which may in turn have several different effects on thyroid function. These effects include suppression of thyroid stimulating hormone (TSH) resulting in decreased release of T4 from the thyroid gland, and inhibition of 5'-deiodinase I, thereby decreasing the peripheral conversion of inactive T4 to active T3.[31] In addition, reverse T3 (rT3) is increased, at least in the acute stress response. Chronic stress can also result in hypoactivation or suppression of the hypothalamo-pituitary-adrenal axis, causing a decrease in cortisol releasing hormone (CRH). This in turn results in the decrease in glucocorticoid production and a secondary increase in auto-immune disorders such as Hashimoto's thyroiditis.[31]

The relationship of hypothyroidism to muscle pain is complex because there is a controversy over the mechanism of so-called hormone resistant hypothyroidism due to peripheral blocking of T3 activity, and over its relationship to the development of myalgia. Few would argue about whether hypothyroidism associated with an elevated TSH should be treated. In normal individuals whose TSH levels are under two units, slight elevations of the TSH often indicate mild hypothyroidism. These patients often complain of fatigue, feel cold, tend to be constipated, have dry skin, and muscle pain. Treatment with a thyroid supplement that reduces the TSH level to 1.5 units or less will often improve these symptoms, and render the muscle more responsive to treatment. A controversy exists over whether hypothyroidism responsive to large doses of T3 is a factor that causes chronic muscle pain such as FMS.[32,33] Specifically, the issue is whether reverse T3 blocks the effect of T3 at the cellular level, thereby creating a peripheral hypothyroidism unrelated to hypothalamic or thyroid gland function. There are conflicting data regarding the metabolic activity of rT3, and its action as an inhibitor of T3, capable of producing a hypometabolic state. Another view is that rT3 is metabolically inactive, but is a marker for down regulation of the thyroid axis. In this situation, elevation of rT3 signals an impairment of the feedback mechanism in which TSH rises when T3 concentrations fall. These issues are important in both MPS and FMS, because there are reasons to believe that rT3 is increased in both conditions.

b) Hypothyroidism and chronic and critical illness

Clinical hypothyroidism with normal levels of T3, T4 and TSH occurs in the so-called sick euthyroid state often seen in chronic illness or in the Intensive Care Unit in prolonged critical illness. This condition, also known as non-thyroidal illness, has bearing on the postulated hypothyroid hypometabolic state of FMS, with normal laboratory parameters of thyroid function (TSH, T3, T4). This issue has not been addressed so directly in MPS, but if both MPS and FMS, when chronic, have a similar underlying basis of central hypersensitivity, and if both are initiated by an acute or recurring energy crisis, then a postulated hypothyroid hypometabolic state becomes relevant in both conditions.

Tissue thyroid levels are reduced in prolonged critical illness. Evidence suggests that there is a central neuro-endocrine failure, at least in part at the level of the hypothalamus, based on the continued responsiveness to other factors such as growth hormone.[34] On the other hand, non-thyroidal illness syndrome with low levels of T3 and T4 can be an acute response to stress. Possible causes of this phenomenon range from a decrease in the deiodination of tetra-iodothyroxine by 5'-deiodinase to make tri-iodothyroxine, inhibition of T4 and T3 binding proteins, or the action of circulating cytokines. A study of healthy individuals undergoing elective abdominal surgery explored the response of thyroid function to acute stress. There was a decline of T3 starting 30 minutes before the skin incision was made that continued throughout the postoperative observation

period. An early rise in TSH attenuated the decline of T3 after eight hours. T4 rose soon after the skin incision and remained elevated. Reverse T3 rose six hours after surgery and remained elevated. Serum cortisol levels rose rapidly after entering the operating suite and remained high thereafter. Cytokine responses were mixed, interleukin-6 (IL-6) rising two hours after skin incision and tumour necrosis factor alpha (TNF-1 alpha) not rising at all. The rapid rise in cortisol was hypothesised to cause the fall in T3 in this acute syndrome.[35] In another study of the euthyroid sick syndrome that was created experimentally by isolated limb perfusion with TNF-alpha, there was a rapid fall in T3, rT3, T4 and thyroxine-binding globulin (TBG), whereas free T4 (fT4) showed a sharp rise. T3 remained low, but rT3 rose over 24 hours. TSH declined initially, but rose progressively to greater than pre-perfusion levels and remained elevated over one week. Cortisol or IL-6 was thought to be related to the decline in T3 and T4 levels. Recovery was thought to be TSH dependent, because its rise preceded the rise of T4 and T3.[36] Thus, in the sick euthyroid syndrome, the decline in T3 function appears to be related to an initial fall in T3 levels, and a decline in the conversion of T4 to T3, and might be a response to a rise in cortisol levels.

c) Role of reverse T3

The role of rT3 in non-thyroidal illness remains unclear. Changes in rT3 may be a marker of non-specific response to acute or chronic stress. For example, rT3 was elevated in females with ankylosing spondylitis, whereas FT3 and FT4 and total T3 were significantly lower. TSH and total T4 were normal. Antithyroid antibodies were elevated as well.[37] TSH response to thyrotropin releasing hormone (TRH) was normal. It was not stated in this study whether the AS subjects were clinically hypothyroid. The controversy is whether rT3 is metabolically active or not, and if it is an inhibitor of T3, thereby producing a hypometabolic state. The alternative view is that rT3 is metabolically inactive, but is a marker for down-regulation of the thyroid axis as illustrated in the above study. In this view, elevation of rT3 indicates that the feedback mechanism in which TSH rises in response to lowering of T3 is impaired. This controversy is important in both MPS and FMS, because there are reasons to believe that rT3 is increased in both conditions.

This question of the role of rT3 has been looked at in non-myalgic illness. Reverse T3 has been shown to be a marker for increased mortality after acute myocardial infarction.[38] T3 was slightly reduced in the myocardial infarction group, rT3 was considerably increased, and T4 was slightly increased, signifying reduced conversion of T4 to T3. TSH was slightly lower in the MI patients than in the controls. However, only the increased levels of rT3 and T4 correlated with increased mortality. Despite reports that intravenous T3 was beneficial in animal studies of myocardial infarction, T3 administration to patients undergoing cardiac bypass surgery did not improve outcome.[38] The authors speculated that rT3, usually considered to be an inactive metabolite, has biologic activity, perhaps as a competitive inhibitor of T3.

On the other hand, a study correlating molecular modelling of thyroid hormone metabolites with the known inhibition of gamma-aminobutyric acidA (GABAA) by T3 showed only a weak effect of rT3, and made the point that the molecular configuration of rT3 was less rigid than native T3, so that there is greater flexibility between the two aromatic rings, thereby affecting ion channel activity and GABAA activity.[39] This study suggests that rT3 is biologically inactive at least some of the time. Finally, it is thought that in inflammatory stress conditions, cytokines can also inhibit the production of TSH.[31]

The question of the relationship of the factors that produce a hypometabolic state to chronic myalgia as a result of stress will now be addressed. Hypothalamic-pituitary-adrenal axis response to stress has been well studied in the acute stress state. Disorders of this axis have been implicated in the development of FMS.[13] The acute state is associated with activation of the hypothalamic-pituitary-adrenal axis and an increase in CRH. Glucocorticoids are increased, suppressing the immune system, and by a feedback mechanism, lead to termination of the acute stress response. Moreover, glucocorticoids also decrease growth hormone secretion and inhibit somatomedin C, both phenomena known to occur in FMS, but not really well studied in MPS. The adrenergic system (locus coeruleus-norepinephrine system) is also activated. Release of beta-endorphins from the hypothalamus in the acute stress response suppresses pain perception. Activation of the hypothalamic-pituitary-adrenal system also centrally

suppress TSH production and inhibit the peripheral conversion of T4 to T3, producing the non-thyroidal illness syndrome. Cytokines are potent activators of the stress response. Tumour necrosis factor alpha (TNF-alpha), IL-6 and interleukin 1 alpha are known to stimulate the hypothalamic-pituitary-adrenal system. They have also been implicated in inhibiting thyroid function.[40,41]

As suggested by the above studies, rT3 elevation is a non-specific response to both chronic illness and acute stress. The question remains unanswered whether rT3 is functioning as a blocker to the action of T3 by competing for T2 receptors at the cellular level, resulting in hypothyroidism, and whether such an effect, if present, can be overcome by increasing TSH levels or by T3 supplementation.

d) Growth hormone deficiency

Growth hormone (GH) deficiency has been associated with FMS. Measurements of insulin-like growth factor-1 (IGF-1) show a deficiency in about 30% of FMS patients.[42] GH deficiency syndromes share many characteristics with FMS. GH secretion may be impaired secondary to a variety of physical and psychological stressors. It is a treatable condition, and therefore worth investigating in FMS who do not have other identifiable causes or co-morbidities. Whether patients with FMS and GH deficiency have one disease (GH deficiency), or have FMS made worse by GH deficiency, is a moot point. The point made by Bennett is that treatment with GH results in clinical improvement.[42] However, a study of premenopausal women showed no association between FMS and IGF-1 casting doubt on the validity of this association in this age group.[43] The authors point out that older age and obese populations have lower activity of the GH-IGF-1 axis, and that these conditions must be considered when studying the GH-IGF-1 axis in FMS subjects. Thus, it can be said that GH deficiency produces a syndrome much like FMS, but it is far from clear whether a subset of FMS patients can be said to have FMS as a result of impaired GH secretion. Moreover, the sub-populations of FMS patients where this might apply have yet to be defined.

Other conditions

A study of the connective tissue disorder systemic lupus erythematosis (SLE) and fibromyalgia showed that nearly 10% of Caucasians had FMS, about 2-3 times the expected prevalence in the general population. The prevalence was much lower in African-Americans and in Hispanics, with an overall prevalence of 5%, a little more than has been reported in general studies (2-4% prevalence in various studies). FM correlated best with Caucasian ethnicity, anxiety, or affective disorder. It did not correlate with SLE clinical activity, specific organ damage, or serologic features.[4] Thus, SLE is appropriately considered in the Caucasian sub-population of FMS patients. However, it is unknown in how many SLE patients SLE is the presenting manifestation. Moreover, the course of FMS and SLE do not seem to be related necessarily.

Finally, the relation of chronic infection to myalgia (both MPS and FMS) is interesting. The investigation of specific conditions is warranted when the history is compatible with such a diagnosis. This concept was dramatically illustrated in a competitive athlete who swam in ponds and lakes throughout the United States over a period of time. This athlete complained of fatigue and diffuse muscle pain. Two protozoan infections, including amoebiasis, and Lyme disease were found. Chronic Lyme disease was the specific factor causing muscle pain and fatigue. Common considerations in the United States include parasitic infections, Lyme disease, chronic mycoplasma infections, and enteroviruses.

Chronic Lyme disease can present with a combination of myalgia and arthralgia, fatigue and impaired cognition, all features seen with FMS. Treatment of such persons is difficult. The chronic state, sometimes referred to as Post-Lyme disease syndrome or Post-treatment Lyme disease syndrome, failed to show an improvement in cognition, but did show improvement in fatigue, after prolonged treatment with either 30 days intravenous ceftriaxone followed by oral doxycycline, or 28 days of intravenous ceftriaxone.[45,46] However, macrolide antibiotics are less active at acidic pH, and poor responses such as those just cited, may be due to localisation of the spirochete in an acidic endosome. Macrolide antibiotic activity, but not that of the tetracyclines, may be enhanced by alkalinisation with hydroxycholoquine.[47] Other diseases that look like Lyme disease, but that are treated differently, like Babesiosis and Ehrlichiosis, should also be considered in persistent and difficult cases.

Enterovirus infection has been investigated in FMS and chronic fatigue syndrome (CFS) patients by polymerase chain reaction (PCR) assays of muscle biopsy tissue. A number of studies have shown a significant increase in the prevalence of PCR positive samples for enterovirus, and positive neutralising antibody for Coxsackie B virus, in patients with chronic fatigue syndrome, ranging for 20% to 58%, compared to controls showing 0-9% positive.[48,49] In one study of FMS patients, 13% (4 out of 30) were positive for enterovirus, compared to none of 29 controls.[50] However, another study failed to show evidence to support a role of persistent enteroviral infection in CFS patients, but could not exclude the possibility of such an infection being an initiating factor.[51] This is an interesting etiologic consideration, but as of now, of little practical clinical use, since muscle biopsy is not routinely done in FMS patients, and there is no specific treatment for enterovirus infection.

Investigations

The history gives clues about structural and metabolic or nutritional problems that lead to further, focused examinations. The physical examination is the place to look for scoliosis, leg length inequality, pelvic torsion, and hypomobility and hypermobility of joints. Imaging studies are often not necessary for this purpose, though they play an important role in identifying co-morbid conditions. Laboratory tests are necessary to identify metabolic, hormonal or nutritional disorders that are important in chronic myalgia. Depending on the direction of investigation suggested by the history and physical examination, the laboratory tests in Table 4 are useful in the evaluation of chronic myalgia, including both MPS and FMS. Generalised or widespread muscle pain is more likely to be metabolic, whereas structural or mechanical factors are often seen with focal myalgias. The exception is hypermobility syndromes that can be associated with generalised MPS. Iron insufficiency is usually restricted to women, and is generally seen in men only when there has been gastrointestinal blood loss from ulcers or cancer, or from taking non-steroidal anti-inflammatory drugs. Vitamin B12 deficiency is far more prevalent than one might think, and approaches 15 percent of persons with chronic MPS. Metabolic abnormalities can be seen at levels as high as 350pg/ml. Folic acid metabolism is closely linked to that of vitamin B12, and should also be measured. Other vitamin deficiency states such as vitamin C and vitamins B1 and B6 can also be associated with widespread myalgia. Vitamin D levels below 32pg/ml have been found to be associated with musculoskeletal pain. Hypothyroidism is a major consideration because it produces a hypometabolic state thought to promote trigger point formation. Values of thyroid stimulating hormone (TSH) in the upper half of the normal range (above 2.5

Table 4 **Laboratory investigations for chronic FMS and MPS**

	investigation	comment
1	Serum ferritin	tissue stores are depleted at levels of 15-20ng/ml
2	Serum vitamin B12	impairment at levels as high as 350pg/ml. Follow-up testing includes serum methylmalonic acid and homocysteine. Either may be elevated in vitamin B12 deficiency
3	Serum and erythrocyte folic acid	folic acid metabolism is closely linked to vitamin B12 action
4	Thyroid stimulating hormone (TSH)	normally generally below 2.5 ISU. Careful history and physical examination often show signs of hypothyroidism in persons whose TSH level is in the upper normal range
5	25-hydroxy vitamin D	levels below 32ng/ml are seen in symptomatic individuals
6	Lyme disease	ELISA confirmed by Western blot. Also test for Ehrlichiosis, Babesiosis and Bartonella – may simulate Lyme Disease or co-exist with it
7	Hepatitis C	
8	Ova and parasites	
9	Insulin growth factor-1	
10	Vitamins C, B1 and B2	
11	C-reactive protein	
12	Antinuclear antibodies	

international standard units) should lead to careful evaluation of possible clinical hypothyroidism. Infectious diseases can cause widespread pain, particularly Lyme disease. Hepatitis C has been associated with fibromyalgia. Connective tissue diseases such as lupus erythematosus have also been associated with FMS.

Treatment

Treatment of myofascial pain requires the inactivation of MTrPs, the restoration of normal muscle length, and the elimination or correction of the factors that created or perpetuated the trigger points in the first place. Manual therapy to do this includes trigger point compression, often accompanied by a short excursion of the appropriate body part actively to slightly lengthen and shorten the muscle. MTrP pain will usually subside within 20-30 seconds, the referred pain will disappear, and finally the taut band will relax, if not go away, within about a minute. The taut band of muscle is stretched locally along its long axis for a distance of a few inches. This local stretch is not across a joint. A myofascial release technique is applied to the muscle to stretch the fascia, moving over the skin away from the trigger point. A larger range therapeutic stretch is applied, to stretch the muscle across the joint or joints associated with the muscle, e.g. the hip and knee for the rectus femoris muscle. These stretches must be muscle specific to be most effective.

MTrPs can also be inactivated by inserting a needle into the trigger zone or point (Figure 1). This can be done with or without the injection of local anaesthetic.[52] Properly done, a local twitch response will occur, often with a momentary reproduction of referred pain, and then the taut band will relax and tenderness will diminish or disappear. In either case, inactivation by needling or injection, or by manual (physical) therapy, must be followed by correction of mechanical or structural stresses such as forward displaced shoulders and a forward head position, or by pelvic rotation or sacroiliac joint dysfunction. There is no evidence to support the injection of other materials such as steroids or ketorolac. In fact, intramuscular stimulation, a term coined by Gunn,[53] or dry needling, works well, and may work as well as the injection of local anaesthetic, but adequate studies to support one position or the other are lacking. Superficial dry needling, a technique in which the needle is inserted into subcutaneous tissues about 4mm overlying the trigger point, is another means whereby the myofascial trigger point can be inactivated.[54,55] Acupuncture has also been used to treat myofascial pain syndrome. There are few controlled or blinded studies to rely upon. However, there is some indication that acupuncture may be effective in treating some myofascial pain syndromes.[56]

Ergonomic work factors and psychological stresses that may cause or aggravate trigger point formation and activation must also be addressed and corrected or alleviated. Once trigger point pain is reduced and perpetuating factors are addressed, a physical conditioning programme can strengthen muscle, increase endurance, and perhaps reduce the possibility of reactivating the trigger points.

Conclusion

Patients with myalgia can have many co-morbid conditions that perpetuate or aggravate their muscle pain. Such conditions may cause myalgia in the first place, or interfere with the recovery or treatment process. Identification of such conditions should be undertaken in all chronic cases of myalgia. In some cases, an obvious structural abnormality can be identified by physical examination. In other cases, detailed history-taking and laboratory examination may be required. Multiple co-morbidities are not uncommon, particularly the combination of a structural imbalance and a medical condition.

Reference list

1. Gerwin RD, Dommerholt J, Shah JP. An expansion of Simons' integrated hypothesis of trigger point formation. *Curr Pain Headache Rep* 2004;8(6):468-75.
2. Shah J, Phillips T, Danoff JV, Gerber L. A novel microanalytical technique for assaying soft tissue demonstrates significant quantitative biochemical differences in 3 clinically distinct groups: normal, latent, and active. *Arch Phys Med Rehabil* 2003;84:A4.
3. Andreu AL, Hanna MG, Reichman H, Bruno C, Penn AS, Tanji K, et al. Exercise intolerance due to mutations in the cytochrome b gene of mitochondrial DNA. *N Eng J Med* 1999;341(14):1037-44.
4. Wolfe F, Smythe HA, Yunus MR, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatolgy 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee *Arthritis Rheum* 1990;33(2):160-72.
5. Gerwin, RD. Differential diagnosis of myofascial pain syndrome and fibromyalgia. *J Musculoskelet Pain* 1999; 7(1/2):209-15.

6. Bennett RM. Emerging concepts in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia. *Mayo Clin Proc* 1999;74(4)385-98.
7. Gerwin RD. Myofascial and visceral pain syndromes: visceral-somatic pain representations. *J Musculoskelet Pain* 2002;10(1/2): 165-75.
8. Russell, I. J. (2001). Fibromyalgia Syndrome. In: Mense S, Simons DG editors. *Muscle Pain: Understanding its Nature, Diagnosis and Treatment*, Baltimore, Lippincott, Williams & Wilkins: 2001. p289-337.
9. Staud R. Evidence of involvement of central neural mechanisms in generating fibromyalgia pain. *Curr Rheumatol* Rep 2002:4(4)299-305. Review.
10. Price DD, Staud R, Robinson ME, Mauderli AP, Cannon R, Vierck CJ. Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. *Pain* 2002;99(1-2):49-59.
11. Berglund B, Harju EL, Kosek E, Lindblom U. Quantitative and qualitative perceptual analysis of cold dysesthesia and hyperalgesia in fibromyalgia. *Pain* 2002;96(1-2):177-87.
12. Martinez-Lavin MA, Hermosillo AG, Mendoza C, Ortiz R, Cajigas JC, Pineda C et al. Orthostatic sympathetic derangement in subjects with fibromyalgia *J Rheumatol* 1997;24(4):714-8.
13. Dessein PH, Shipton EA, Stanwix AE, Joffe BI. Neuroendocrine deficiency-mediated development and persistence of pain in fibromyalgia: a promising paradigm? *Pain* 2000;86(3):213-5.
14. Cronan TA, Serber ER,Walen HR, Jaffe M. The influence of age on fibromyalgia symptoms. *J Aging Health* 2002;14(3):370-84.
15. Heymann RE, Helfenstein M, Feldman D. (2001). A double-blind, randomized, controlled study of amitriptyline, nortriptyline and placebo in patients with fibromyalgia. An analysis of outcome measures. *Clin Exp Rheumatol* 2001;19(6):697-702.
16. Jones KD, Burckhardt CS, Clark SR, Bennett RM, Potempa KM. A randomized controlled trial of muscle strengthening versus flexibility training in fibromyalgia. *J Rheumatol* 2002;29(5):1041-8.
17. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. **JAMA** 2004;292(19):2388-95.
18. Mense S, Simons DG, Russell IJ. *Muscle Pain: understanding its nature, diagnosis and treatment.* Philadelphia: Lippincott Williams & Wilkins; 2001.
19. Simons DG, Travell JG, Simons LS. *Myofascial Pain and Dysfunction: The Trigger Point Manual*. 2nd edition. Baltimore, Lippincott, Williams & Wilkins;1999.
20. Gerwin RD, Shannon S, Hong CZ, Hubbard D, Gevirtz R. Interrater reliability in myofascial trigger point examination. *Pain* 1997;69(1-2):65-73.
21. Chen JT, Chen SM, Kuan TS, Chung KC, Hong CZ. Phentolamine effect on the spontaneous electrical activity of active loci in a myofascial trigger spot of rabbit skeletal muscle. *Arch Phys MedRehabil* 1998;79(7):790-94.
22. Baik HW, Russell RM. Vitamin B12 deficiency in the elderly. *Annu Rev Nutr* 1999;19:357-77.
23. Andres E, Loukili NH, Noel E, Kaltenbach G, Abdelgheni MB, Perrin AE et al. Vitamin B12 (cobalamin) deficiency in elderly patients. *CMAJ* 2004;171(3):251-9.
24. Hallberg L, Hulthen L. Perspectives on iron absorption. *Blood Cells Mol Dis* 2002;29(3):562-73.
25. Sun ER, Chen CA, Ho H, et al. Iron and the restless leg syndrome. *Sleep* 1998;21,371-77.
26. Kotagal S, Silber MH. Childhood-onset restless legs syndrome. *Ann Neurol* 2004;56(6):803-7.
27. Glerup H, Mikkelsen K, Poulsen L, Hass E, Overbeck S, Anderson H, et al. Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. *Calcif Tissue Int* 2000;66(6):419-24.
28. Mascarenhas R, Mobarhen S. Hypovitaminosis D-induced pain. *Nutr Rev* 2004;62(9):354-9. Review.
29. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, non-specific musculoskeletal pain. *Mayo Clin Proc* 2003; 78(12):1463-70.
30. Sorvillo F, Massiotti G, Carbone A, Morisco F, Cioffi M, Rotundi M, et al. Increased serum reverse triiodothyronine levels at diagnosis of hepatocellular carcinoma in patients with compensated HCV-related liver cirrhosis. *Clin Endocrinol* (Oxf) 2003;58(2):207-12.
31. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *J Psychosom Res* 2002;53(4):865-71. Review.
32. Garrison RL, Breeding PC. A metabolic basis for fibromyalgia and its related disorders: the possible role of resistance to thyroid hormone. *Med Hypotheses* 2003;61(2):182-9. Review.
33. Lowe JC. Thyroid status of 38 fibromyalgia patients:implication for the etiology of fibromyalgia. *Clin Bull Myo Ther* 197;2:36-41.
34. Van den Berghe G, de Zegher F, Baxter RC, Veldhuis JD, Wouters P, Schetz M, et al. Neuroendocrinology of prolonged critical illness: effects of exogenous thyrotropin-releasing hormone and its combination with growth hormone secretagogues. *J Clin Endocrinol Metab* 1998;83(2):309-19.
35. Michalaki M, Vagenakis AG, Makri M, Kalfarentzos F, Kyriazopoulou V. Dissociation of the early decline in serum T(3) concentration and serum IL-6 rise and TNFalpha in nonthyroidal illness syndrome induced by abdominal surgery. *J Clin Endocrinol Metab* 2001;86(9);4198-205.
36. Feelders RA, Swask AJ, Romijn JA, Eggermont AM, Tielens ET, Vreugdenhil G, et al. Characteristics of recovery from the euthyroid sick syndrome induced by tumor necrosis factor alpha in cancer patients. *Metabolism* 1999;48(3):324-29.
37. Lange U, Boss B, Teichmann T, Klett R, Stracke H, Bretzel RG, et al. Thyroid disorders in female patients with ankylosing spondylitis. *Eur J Med Res* 1999;4(11):468-74.
38. Friberg L, Drvota V, Bjelak AH, Eggersten G, Ahnve S. Association between increased levels of reverse triiodothyronine and mortality after acute myocardial infarction. *Am J Med* 2001;111(9):699-703.
39. Martin JV, Padron JM, Newman MA, Chapell R, Leidenheimer NJ, Burke LA. Inhibition of the activity of the native gamma-aminobutyric acid A receptor by metabolites of thyroid hormones: correlations with molecular modeling studies. *Brain Res* 2004;1004(1-2):98-107.
40. Witzke O, Winterhagen T, Saller B, Roggenbuck U, Lehr I, Philipp T, et al. Transient stimulatory effects on pituitary-thyroid axis in patients treated with interleukin-2. *Thyroid* 2001;11(7):665-70.
41. Jakobs TC, Mentrup B, Schmutzler C, Dreher I, Kohrle J. Proinflammatory cytokines inhibit the expression and function of human type I 5'-deiodinase in HepG2 hepatocarcinoma cells. *Eur J Endocrinol* 2002;146(4):559-66.

42. Bennett RM. Adult growth hormone deficiency in patients with fibromyalgia. *Curr Rheumatol Rep* 2002;4(4): 306-12.
43. McCall-Hosenfeld JS, Goldenberg DL, Hurwitz S, Adler GK. Growth hormone and insulin-like growth factor-1 concentrations in women with fibromyalgia. *J Rheumatol* 2003;30(4):809-14.
44. Friedman AW, Tewi MB, Ahn C, McGwin G Jr., Fessler BJ, Bastian HM, et al. Systemic lupus erythematosus in three ethnic groups: XV. Prevalence and correlates of fibromyalgia. *Lupus* 2003;12(4):274-9.
45. Klempner MS. Controlled trials of antibiotic treatment in patients with post-treatment chronic Lyme disease. *Vector Borne Zoonotic Dis* 2002;2(4):255-63.
46. Kaplan RF, Trevino RD, Johnson GM, Levy L, Dornbush R, Hu LT et al. Cognitive function in post-treatment-Lyme disease: do additional antibiotics help? *Neurology* 2003;60(12):1916-22.
47. Donta ST. Macrolide therapy of chronic Lyme Disease. *Med Sci Monit* 2003;9(11):1136-42.
48. Lane RJ, Soteriou BA, Zhang H, Archard LC. Enterovirus-related metabolic myopathy: a postviral fatigue syndrome. *J Neurol Neurosurg Psychiatry* 2003;74(10):1382-6.
49. Nairn C, Galbraith DN, Clements GB. Comparison of Coxsackie B neutralisation and enteroviral PCR in chronic fatigue patients. *J Med Virol* 1995;46(4):310-3.
50. Douche-Aourik F, Berlier W, Feasson L, Bourlet T, Harrath R, Omar S, et al. Detection of enterovirus in human skeletal muscle from patients with chronic inflammatory muscle disease or fibromyalgia and healthy subjects. *J Med Virol* 2003;71(4):540-7.
51. McArdle A, McArdle F, Jackson MJ, Page SF, Fahal I, Edwards RH. Investigation by polymerase chain reaction of enteroviral infection in patients with chronic fatigue. *Clin Sci (Lond)* 1996;90(4):295-300.
52. Cummings TM, White A. Needling therapies in the management of myofascial trigger point pain: a systematic review. *Arch Phys Med Rehabil* 2001;82(7):986-92.
53. Gunn CC. *The Gunn approach to the treatment of chronic pain*. 2nd ed. New York: Churchill Livingstone; 1996.
54. Baldry PE. *Myofascial pain and fibromyalgia syndromes*. Edinburgh: Churchill Livingstone; 2001.
55. Edwards J, Knowles N. Superficial dry needling and active stretching in the treatment of myofascial pain-a randomised controlled trial. *Acupunct Med* 2003;21(3):80-6.
56. Itoh K, Katsumi Y, Kitakoji H. Trigger point acupuncture treatment of chronic low back pain in elderly patients-a blinded RCT. *Acupunct Med* 2004;22(4):170-7.