Central Sensitization and Neurogenic Inflammation in Relationship to Fibromyalgia

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Abstract

Objective: This literature review is intended to explain the mechanism behind which fibromyalgia exists. The relationship of inflammation as the cause of the widespread pain and tenderness that is felt by those who have this syndrome will be discussed, along with sources of that inflammation, as well as possible treatment methods for fibromyalgia.

Data Collection: A computer search using the databases PubMed and EBSCOHost generated articles relevant to central sensitization, neurogenic inflammation, and fibromyalgia. The selection strategy included free full text articles that were available from Logan Online. Sources were referenced from individual searches and from an overall review of the literature. The following are articles that were chosen: articles discussing the process of central sensitization and neurogenic inflammation, articles discussing the mechanism of fibromyalgia, articles of studies performed regarding pain threshold in those with fibromyalgia, articles about chronic pain, and articles about treatment of fibromyalgia

Data Synthesis: Fibromyalgia is a chronic pain syndrome that has been around for centuries. It involves central sensitization and neurogenic inflammation. Understanding these physiological relationships in the production of pain is important in determining appropriate treatment.

Conclusion: Research supports the concept of central sensitization and neurogenic inflammation as main contributors to fibromyalgia. Increasing evidence is demonstrating that diet is a large component of the inflammatory process that leads to the chronic pain involved with this pathology. Additional research needs to be performed to determine the best course of treatment. It appears that pharmaceuticals may cause other symptoms while not providing a lasting effect; while chiropractic care may prove to have lasting benefits without adverse reactions by patients.

Key Words: central sensitization, neurogenic inflammation, fibromyalgia

Introduction

This literature review will discuss the effects of central sensitization and neurogenic inflammation in relationship to fibromyalgia. The research will address the mechanism of central sensitization, how it creates neurogenic inflammation, and how this relates to the diagnosis of fibromyalgia. Sources of inflammation, especially nutritional factors specific to fibromyalgia, will be examined in regards to how they promote or inhibit the inflammatory process.

Fibromyalgia is a chronic pain syndrome that is characterized by widespread pain and diffuse musculoskeletal tenderness. The standard indication is that people suffering from this condition have tenderness at 11 of the 18 specified points throughout their body. The reference points are symmetrically located at the occiput, lower cervical region, trapezius, supraspinatus, second rib, lateral epicondyle, gluteus, greater trochanter and medial fat pad of the knee. The examiner uses their thumb over each spot while applying increasing pressure. If tenderness is felt by the person with less than 4 kg of pressure applied by the examiner then it is considered positive. Additional symptoms of the syndrome include difficulty sleeping, stiffness, fatigue, irritable bowel syndrome (IBS), and allodynia, which is the perception of pain from a non-painful stimulus (1, 2).

Fibromyalgia is a pain syndrome that is categorized as nociceptive. The majority of pain complaints that are addressed clinically arise from this mechanism of pain (3). Nociception is defined as the physiologic response to tissue damage or prior tissue damage (4). This type of widespread chronic pain can be due to central sensitization. Sensitization is when nociceptor thresholds are lowered (3). Therefore, central sensitization involves a hyper-excitability of central nervous system neurons. This leads to hyperalgesia, which is an exaggerated perception

of painful stimuli, and allodynia across multiple segments of the body (5, 6). Sensitization can be activated by several mechanisms, some of which include wind-up, also known as temporal summation, dysregulated descending inhibitory pathways, and upregulated facilitatory modulation (5).

It is believed that activation of pain receptors, transmission and modulation of pain signals, neuroplasticity, and central sensitization are all part of the inflammatory response (7). Therefore, all pain, including that which is felt by those who suffer from fibromyalgia, may prove to have its' roots in inflammation and the inflammatory response.

Inflammation

4 Cardinal Signs of Inflammation

The inflammation system is in many ways looked upon as the classic biological stimulation-response system. This is because the innate immune system, followed by the adaptive immune system, responds to invading microorganisms. This stimulation-response activity promotes various aspects of inflammation, including large amounts of cytokine production, activation of multiple cell types, and the four cardinal signs of inflammation. The four cardinal signs of inflammation include calor, dolor, rubor, and tumor. These are otherwise known as heat, pain, redness, and swelling, respectively. However, the inflammation system is also considered a classic homeostatic system too, since it functions each moment to maintain organ and organism function. Therefore, inflammation appears to serve a dual function; as both a stimulation-response and homeostatic system. This dual function system raises the question of whether C-reactive protein (CRP), part of the innate immune system; fibrinogen, part of the coagulation system; and interleukin-6 (IL-6), a proinflammatory cytokine mediator; represent typical homeostatic function or serve as a response to pathological conditions. Research indicates that

these biomarkers do both, likely to varying degrees in different people and in the same person at different times under different conditions. This is implying that in younger, healthier people, the biomarkers represent more of an ongoing homeostatic function; whereas, increasing age is accompanied by increasing input from chronic pathological processes leading to a stimulation-response function of inflammation as a result of increased disease burden (17).

Types of Inflammation:

Acute

Acute inflammation begins instantly following the injury of tissues. It is the body's normal protective response to injury or irritation. There are three main processes that occur throughout this defense process. They include increased blood flow, increased permeability of the capillaries, and migration of neutrophils. Increased blood flow is due to dilation of blood vessels supplying the region. Increased permeability of the capillaries is to allow fluid and blood proteins to move into the interstitial spaces. And migration of neutrophils and possibly macrophages out of the venules is so that they can go into the interstitial spaces (18).

Immunogenic

Immunogenic inflammation is the result of an antigen binding to an antibody or leukocyte receptor to trigger an inflammatory cascade. Prior sensitization is required and the inflammatory response can take several forms. These forms include immediate and cell-mediate hyper-sensitivity (19).

Neurogenic

Neurogenic inflammation is when a chemical combines with the chemical irritant receptors on sensory nerves, leading to the release of substance P and other inflammatory neuropeptides (19, 20). It can also occur when a nerve impulse travels down an axon to release

substance P at the terminus (19, 21, 22). Neurogenic inflammation describes the nervous systems participation in the inflammatory and disease process. Research suggests that most inflammatory diseases and pain syndromes are driven by neurogenic inflammation (23).

Relationship Between the Different Types of Inflammation

There is significant crossover between immunogenic and neurogenic inflammation since substance P can degranulate mast cells and histamine can activate sensory nerves (24). Clinically, the two forms may lead to the same end result. Foreign materials can produce inflammation in a tissue through both of these interrelated systems. In fact, an interesting feature of the inflammation response is that a stimulus in one tissue can lead to inflammation at another site, known as neurogenic switching. This process where stimulation of inflammation at one site can lead to inflammation at another site involves an exposure to either an allergen or chemical irritant at one site leading to a sensory nerve impulse. With allergens, mast cell degranulation occurs. This results in antigen binding IgE molecules on mast cells to release histamine and other mast cell mediators. This histamine binds to receptors on sensory neurons. With chemical irritants, receptors on peripheral nerves are directly triggered by the binding of sensory neurons. When the afferent signal reaches the central nervous system, it is redirected to another peripheral location, leading to the release of substance P and other neuropeptides. This produces inflammation at the second site. Histamine can bind to receptors on sensory neurons, and substance P can bind to receptors on mast cells. Both histamine and substance P can bind effector cells, such as endothelial cells, mucus-secreting cells, and bronchial smooth muscle cells to produce inflammation. Therefore, neurogenic switching occurs when an efferent signal from the central nervous system causes release of neuropeptides at another site, producing inflammation at the second site without local stimulation (19).

Disease Correlation

Neurogenic switching provides an explanation for many different illnesses and diseases. Food allergy is one example. When a food allergen is ingested it can produce gastrointestinal symptoms with diarrhea, abdominal pain, bloating, and emesis. This is due to the direct degranulation of gut mast cells with local mediator release. However, some patients with food allergies will develop symptoms at other sites, manifesting as asthma (25), rhinitis (26), or urticaria (27). This type of food hypersensitivity can also present as arthritis (28, 29) and migraine (30, 31). As described earlier, this is a result of histamine from the gut mast cells binding to sensory nerves to produce an afferent signal, which is rerouted by the central nervous system to another site (19).

Another example is systemic anaphylaxis. Multiple organ systems are affected immediately, such as: respiratory involvement with bronchospasm, bronchorrhea, and laryngeal edema; gastrointestinal symptoms; skin involvement away from the site of inoculation; and cardiovascular symptoms with hypotension from vasodilation (19).

Neurogenic switching may also play a role in multiple chemical sensitivity syndrome (32, 33, 34), which is thought to be mediated by neurogenic inflammation (35). This syndrome is characterized by exposure to respiratory irritants triggering symptoms in more than one organ system. Individuals with chemical sensitivities usually have recurrent sites of symptomatology and inflammation which reoccur with a well-defined pattern. Some examples of these sites include myalgias in the nape of the neck, inflammation of a particular set of joints, or gastrointestinal symptoms occurring repeatedly. Therefore, the creation of a neuronal pathway so that stimulation of irritant receptors in the airway leads to inflammation in a given tissue may be the mechanism for involvement of secondary organ systems (19).

In addition, neurogenic inflammation is thought to play a role in rheumatoid arthritis (36), migraine headache (37, 38), and fibromyalgia (39). These conditions may be due to an acquired neuronal pathway that shunts inflammatory stimuli to the joints, cerebral vasculature, or muscles. Then, inflammatory stimuli arising from allergens, chemical irritants, or infectious agents could lead to a flare in inflammation at the diseased site. Emotional stress might also lead to neuronal signals that could result in inflammation at susceptible sites (19).

Neurogenic Inflammation

Mechanisms of Central Sensitization

Nociception is defined as the physiologic response to tissue damage or prior tissue damage (4). This type of widespread chronic pain can be due to central sensitization. Sensitization is when nociceptor thresholds are lowered (3). Therefore, central sensitization involves a hyper-excitability of central nervous system neurons. This leads to hyperalgesia, which is an exaggerated perception of painful stimuli, and allodynia across multiple segments of the body (5, 6).

The International Association for the Study of Pain states that "pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (40). According to Winkelstein, there are a number of physiologic mechanisms by which injuries lead to nociceptive responses and ultimately to pain (4). Nociceptive input mainly activates two types of pain receptors. These include low-threshold nociceptors and high-threshold nociceptors. The low-threshold nociceptors are connected to A-delta pain fibers, which are fast conductors, and the high-threshold nociceptors are connected to C-fibers, which are slow, unmyelinated conductors. These A- and C-pain fibers synapse with spinal neurons in the dorsal horn of the spinal cord by way of synaptic transmission. Many neurotransmitters are

then able to modulate the postsynaptic responses with further transmission to supraspinal sites by way of the ascending pathways (4, 41, 42).

The simplest form of plasticity in nervous systems is that repeated noxious stimulation may lead to habituation, which is a decreased response, or sensitization, which is an increased response (43). Therefore, prolonged or strong activity of dorsal horn neurons caused by repeated or sustained noxious stimulation may lead to increased responsive of the neurons, or central sensitization (42, 44). This neuroplasticity followed by central nervous system sensitization includes altered function of chemical, electrophysiological, and pharmacological systems (4, 45). These changes cause hyperalgesia, allodynia, and may be involved in the generation of referred pain and hyperalgesia across multiple spinal segments (42, 46, 47, 48, 49). Sensitization can be activated by several mechanisms, some of which include wind-up, also known as temporal summation, dysregulated descending inhibitory pathways, and upregulated facilitatory modulation (5).

Nociceptive Afferentation Model of C Fibers

Wind-up

Wind-up refers to a central spinal mechanism in which repetitive noxious stimulation results in a slow temporal summation that is experienced in humans as increased pain (50). This wind-up, or second pain, is more dull and strongly related to chronic pain states, and is transmitted through unmyelinated C fibers to dorsal horn nociceptive neurons. During the C-fibers transmitted stimuli, N-methyl-D-aspartate (NMDA) receptors of second-order neurons become activated (5).

NMDA activation induces calcium entry into the dorsal horn neurons (5, 51). This calcium entry into the sensory neurons in the dorsal horn induces activation of nitric oxide (NO)

synthase, which leads to the synthesis of NO (5, 52). The NO can affect the nociceptor terminals and enhance the release of sensory neuropeptides, specifically Substance P, from pre-synaptic neurons, which contributes to the development of hyperalgesia and maintenance of central sensitization (5, 53). Substance P is an important neurotransmitter for a couple of reasons. First, it lowers the threshold of synaptic excitability, resulting in the release of normally silent interspinal synapses and the sensitization of second-order spinal neurons (5, 54). Second, it can extend for long distances in the spinal cord and sensitize dorsal horn neurons at a distance from the initial input site, which results in an expansion of receptive fields and the activation of wide dynamic neurons by non-nociceptive afferent impulses (5, 41).

Dysregulated Descending Inhibitory Pathways

The dorsolateral funiculus appears to be a preferred pathway for descending pain inhibitory systems (5, 55). There is experimental evidence for the existence of descending inhibitory pathways and their connection with central sensitization. There were observations that bilateral lesions of the dorsolateral funiculus in the rat led to a significant decrease in latency for paw withdrawal to noxious stimulus (5, 56). In addition, temporary spinal cord block, lidocaine, caused dorsal horn nociceptive neurons to expand their receptive fields and their responsiveness to afferent input (5, 57). Selective chemical lesion of serotonergic inhibitory neurons in experimentally "inflamed" animals also resulted in demonstrable behavioral "pain" hypersensitivity (5, 56).

Woolf and Salter (58) discuss that a major function of the descending inhibitory pathway is to focus the excitation of the dorsal horn neurons. The effect is to generate a more urgent, localized, and rapid pain signal by suppressing surrounding activity of the neurons. This role is described by Le Bars and Villaneuva (59). They attribute it to the "diffuse noxious inhibitory

controls" (DNIC) phenomenon. This model illustrates that descending pathways reduce the level of irrelevant noise in the system, which results in effectively enhancing the biologically valuable pain signal (5).

Therefore, based on the function of the descending inhibitory pathway and the studies conducted, the suggestion is that disruption of one or more of the elements of the inhibitory system can result in the equivalent of central sensitization (5, 60).

Upregulated Facilitatory Modulation

There are also facilitatory pathways leading from the brainstem. Behavioral evidence shows that forebrain centers are capable of exerting powerful clinically significant influences on various nuclei of the brainstem, which include the nuclei identified as the origin of the descending facilitatory pathway (5, 60). It is believed that the activity that occurs in descending pathways is not constant but can be modulated. Evidence by Dubner and Ren (5, 55) suggests that selective attention to relevant stimuli activated descending pain modulatory systems, turning the balance in favor of facilitation. The dominance of descending facilitation then led to sensitization of second-order neurons (5, 60).

The sensitization of second-order pain pathway neurons was directly related to the strength of attention. Forebrain activities including cognition, emotions, attention, and motivation have influence on the clinical pain experience (5, 60). Therefore, behavioral modulation associated with selective attention utilizes the same forebrain and brainstem structures and mechanisms that are involved in the development, amplification, and maintenance of persistent pain after actual tissue damage and inflammation (5, 55).

As a result, amplification of pain and its extension in the absence of tissue damage is associated to certain personality traits and cognitive styles. Therefore, descending pathways

behavioral and cognitive therapies might also effect synaptic transmission in the spinal cord and thereby have the capacity to prevent or reverse long-term changes of synaptic strength in pain pathways (5, 61).

Fibromyalgia

History

Although Fibromyalgia Syndrome (FMS) is often thought about as a somewhat new illness, it has actually been around for many, many years. For several centuries, the muscle pains were known as rheumatism, and then as muscular rheumatism. Then, in 1904, Sir William Gowers coined the term fibrositis, literally meaning inflammation of fibers, to describe the tender points found in patients with muscular rheumatism. Dr. Hugh Smythe laid the foundation for the modern definition of FMS by describing widespread pain and tender points in 1972. Then, in 1975, the first sleep electroencephalogram study was performed, which identified the sleep disturbaces that accompany fibromyalgia.

In 1976, physicians changed the name of fibrositis to fibromyalgia since there was no evidence of inflammation. The term fibromyalgia meant pain in muscles and tissues, with the literal breakdown as follows: fibro = fibrous tissue, my = muscle, algia = pain. The first controlled clinical study with validation of known symptoms and tender points was established and published in 1981. This study also proposed the first data-based criteria. In 1984, the important concept that FMS and other similar conditions are interconnected was proposed.

Then in 1990, the American College of Rheumatology developed diagnostic criteria for fibromyalgia to be used for research purposes. These criteria soon began to be used by clinicians as a tool to help them diagnose patients. The concept of neurohormonal mechanisms with central sensitization was developed in the 1990s (62).

Today it is believed that activation of pain receptors, transmission and modulation of pain signals, neuroplasticity, and central sensitization are all part of the inflammatory response (7). Therefore, all pain, including that which is felt by those who suffer from fibromyalgia, may prove to have its' roots in inflammation and the inflammatory response afterall.

Signs and Symptomatology

Fibromyalgia is a chronic pain syndrome that is characterized by widespread pain and diffuse musculoskeletal tenderness (1, 2). The patient population consists of a female to male ratio of 9:1, and the most common age group is 45 to 60 years old (63).

Laboratory tests warranted in the initial evaluation of a patient suspected of suffering from fibromyalgia include: a complete blood count, a renal function test, liver enzymes, ESR, CRP, TSH, serum calcium, PTH, rheumatoid factor, EBV, CMV, and HIV. Since there are no specific laboratory findings typical of fibromyalgia, the workup is ordered in the evaluation mainly to exclude alternative differential diagnoses. Tests such as ESR, CRP, and rheumatoid factor are expected to be normal, although fibromyalgia should not be ruled out if they are not. It is important to rule out hyperparathyroidism since it is classically associated with widespread pain. Given that the lab tests are not able to confirm fibromyalgia, it is not a diagnosis of exclusion. It must be diagnosed by its own characteristic features (1).

According to the 1990 Criteria for the Classification of Fibromyalgia by the American College of Rheumatology, there are two criteria that must be met before the diagnosis of fibromyalgia can be made. The first is that there must be a history of widespread pain. Based on their definition, pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain must be present. In their definition, axial skeletal pain

includes cervical spine, anterior chest, thoracic spine, or the low back. In addition, shoulder and buttock pain is considered as pain for each involved side and low back pain is considered lower segment pain (64).

Secondly, pain must be present in at least 11 of 18 tender point sites on digital palpation. These sites include: the occiput, low cervical, trapezius, supraspinatus, second rib, lateral epicondyle, gluteal, greater trochanter, and knee regions. More specifically, the tender points for each of these regions are as follows: the occiput, bilateral, at the suboccipital muscle insertions; the low cervical, bilateral, at the anterior aspects of the intertransverse spaces at C5-C7; the trapezius, bilateral, at the midpoint of the upper border; the supraspinatus, bilateral, at origins, above the scapular spine near the medial border; the second rib, bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces; the lateral epicondyle, bilateral, 2 cm distal to the epicondyles; the gluteal, bilateral, in the upper outer quadrants of the buttocks in the anterior fold of muscle; the greater trochanter, bilateral, posterior to the trochanteric prominence; and the knee, bilateral, at the medial fat pad proximal to the joint line (64).

In addition, the digital palpation should be performed with an approximate force of 4 kg. And for a tender point to be considered "positive", the subject must state that the palpation was painful. "Tender" is not to be considered "painful". For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months and the presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia (64).

Other symptoms of the syndrome include difficulty sleeping, stiffness, fatigue, irritable bowel syndrome (IBS), and allodynia, which is the perception of pain from a non-painful

stimulus (1, 2). According to Omoigui (7), restless leg syndrome, mood disturbances, interstitial cystitis, migraine headaches, temperomandibular joint dysfunction, and disequilibrium including nerve mediated hypotension, sicca syndrome, and growth hormone deficiency.

Pathophysiology of Fibromyalgia

Fibromyalgia is related to sensitization of central nervous system pain pathways. It is a pain amplification syndrome of patients who are highly sensitive to painful and non-painful stimuli. The pathogenesis of fibromyalgia is uncertain since the cause for the heightened sensitivity of fibromyalgia patients is unknown (65). However, most fibromyalgia patients show increased levels of substance P (66, 67), excitatory amino acids (68), and excitatory neurotrophins (69) in the cerebrospinal fluid (CSF), as well as alterations of the hypothalamic-pituitary-adrenal (HPA) axis in response to stressors (70, 71).

Substance P (SP) is an 11-amino-acid neuropeptide, which acts as a neuromodulator by way of the neruokinin-1 (NK 1) receptor. Substance P sensitizes dorsal horn neurons to the effects of other neuromodulators. Although elevated levels of substance P in cerebrospinal fluid is not specific to fibromyalgia, the high cerebrospinal fluid concentrations of substance P represent the most prominent neurochemical abnormality found in fibromyalgia patients (65). According to Murphy and Zemlan (72), significant negative correlations also exist between levels of substance P and serotonin (5-HT), its precursor tryptophan (TRP), and its primary metabolite hydroxyindoleacetic acid (5-HIAA) in the serum of patients with fibromyalgia.

Nerve growth factor (NGF) stimulates the production of substance P in small afferent unmyelinated neurons. Nerve growth factor was found to be elevated in the CSF of patients with primary fibromyalgia, but not in secondary fibromyalgia, which is when a fibromyalgia patient has an associated painful inflammatory condition (73). This suggests that subgroups of

fibromyalgia patients utilize different pain mechanisms. Primary and secondary fibromyalgia share a common link of elevated substance P in cerebrospinal fluid; however, both groups utilize different pathways that result in the increased substance P levels. In patients with primary fibromyalgia, nerve growth factor produced by central interneurons appears to increase substance P. However, in patients with secondary fibromyalgia, the inflammation characteristic for the underlying rheumatic or infectious conditions appears to be responsible for the elevated substance P. Therefore, according to Giovengo, Russell, and Larson (73), it appears that nerve growth factor could be essential for the initiation and/or perpetuation of painful symptoms of primary fibromyalgia but not secondary. It is important to note that central sensitization is associated with the release of excitatory amino acids such as glutamate (GLU), which interacts both with its receptor and with neuropeptides such as substance P and nerve growth factor (65).

The hypothalamic-pituitary-adrenal axis is part of an adaptive system that responds to stressors such as pain and trauma, as well as physiologic stressors. The key regulator of the HPA axis is corticotrophin-releasing hormone (CRH). The mechanisms of the HPA axis in fibromyalgia patients are not completely understood, but it is clear that serotonin plays a critical role. The serotonin neurons projecting from the midbrain raphe nuclei deliver synaptic input to the corticotrophin-releasing hormone neurons in the hypothalamus, which changes the level of corticotrophin-releasing hormone neuronal activity (65).

There is also increasing evidence that indicates dorsal horn glia cells might have a large role in producing and maintaining abnormal pain sensitivity (74, 75). Synapses within the CNS are encapsulated by glia that do not normally respond to nociceptive input from local sites. However, following the initiation of central sensitization, spinal glia cells are activated by a wide array of factors that contribute to hyperalgesia. These factors include immune activation within

the spinal cord, substance P, excitatory amino acids, nitric oxide, and prostaglandins. Once activated, glia cells release proinflammatory cytokines, including tumor necrosis factor, interleukin-6 (IL-6), interleukin-1 (IL-1), nitric oxide, prostaglandins, excitatory amino acids, adenosine triphosphate (ATP), and fractalkine (76). These proinflammatory cytokines further increase the discharge of excitatory amino acids and substance P from the Aβ and C afferents that synapse in the dorsal horn and also enhance the hyperexcitability of the dorsal horn neurons (74, 77).

Given that fibromyalgia is associated with extensive secondary hyperalgesia and allodynia, central sensitization through wind-up appears to play a critical role. When wind-up pain is evoked both in fibromyalgia patients and in normal controls, the perceived pain increase by experimental stimuli and the magnitude of wind-up within a series of stimuli is greater for fibromyalgia patients compared with the control subjects. Following a series of stimuli, wind-up after sensations is also increased, lasts longer, and is more frequently painful in fibromyalgia patients. These results indicate both augmentation and prolonged decay of nociceptive input in fibromyalgia patients and provide strong evidence for central sensitization's role in the pathogenesis of fibromyalgia (65).

Staud and Spaeth (65) indicate that the mechanisms underlying the central sensitization that occurs in patients with fibromyalgia relies on hyperexcitability of spinal dorsal horn neurons that transmit nociceptive input to the brain. As a result, low intensity stimuli delivered to the skin or deep muscle tissue generate high levels of nociceptive input to the brain, as well as the perception of pain. More specifically, intense or prolonged impulse input from Aβ and C afferents sufficiently depolarizes the dorsal horn neurons, which results in the removal of the magnesium block of NMDA-gated ion channels. Following this occurrence, there is an influx of

extracellular calcium and production of nitric oxide, which diffuses out of the dorsal horn neurons. As a result, nitric oxide promotes the exaggerated release of excitatory amino acids and substance P from presynaptic afferent terminals and causes the dorsal horn neurons to become hyperexcitable. Subsequently, low intensity stimuli evoked by minor physical activity may be amplified in the spinal cord resulting in painful sensations.

Nutritional Factors

A study conducted by Sendur, Tastaban, Turan and Ulman (78) examined the association between serum trace elements and clinical findings, such as the number of sensitive tender points, severity of fatigue, and functional status in patients with fibromyalgia. Thirty-two patients diagnosed as having fibromyalgia according to the 1990 Criteria for the Classification of Fibromyalgia by the American College of Rheumatology and thirty-two normal, healthy controls were included in this study.

Serum selenium (mug/dL) and serum zinc (mug/dL) levels were measured by atomic absorption spectrometer. Serum magnesium (mmol/L) level was measured by the original kits of Abbott Aeroset auto-analyzer. The mean age of patients in the fibromyalgia group were calculated as 42.9 (SD = 7.7) years and the mean age of patients in the control group were calculated as 41.3 (SD = 9.7) years. Serum levels of zinc (P = 0.001) and magnesium (P = 0.002) were significantly decreased by the fibromyalgia group. According to the results of this study, it was asserted that serum zinc and magnesium levels may play an important role in the pathophysiology of fibromyalgia.

In addition, according to Holick (79), it is estimated that 40-60% of patients with fibromyalgia may have some component of vitamin D deficiency and osteomalacia. A recent study was done at Medical OPD of Civil Hospital Karachi, from January to March 2009, to

check the vitamin D levels in patients diagnosed with fibromyalgia. Forty female patients that were diagnosed with fibromyalgia according to the 1990 Criteria for the Classification of Fibromyalgia by the American College of Rheumatology and exclusion of systemic illness on examination and normal reports of blood CP, ESR, serum calcium, phosphate, and alkaline phosphatase were included in the study. The mean age of the participants was 37.65 ± 11.5 years. Vitamin D deficiency is defined as less than 20 ng/ml, vitamin D insufficiency is defined as 21-29 ng/ml, and vitamin D sufficiency is defined as equal to or greater than 30 ng/ml. The mean vitamin D level was 17.41±5.497 ng/ml. Thirty-two or 80% of the participants had vitamin D deficiency with mean levels of 15.855±4.918 ng/ml and 8 or 20% of the participants had vitamin D insufficiency with mean levels of 23.64±2.39 ng/ml. The study results further detailed that there were 22 or 68.75% of participants less than 45 years old with a mean vitamin D level of 16.87±4.48 ng/ml and there were 10 or 31.25% of participants 46 to 75 years old that had a mean vitamin D level of 16.09±6.45 ng/ml. As a result of this study, vitamin D deficiency is frequently seen in patients diagnosed with fibromyalgia (80).

It is important to note that according to Seaman (23), neurogenic inflammation is quite possibly the driving force behind pro-inflammatory diseases and lack of healing. According to O'Connor (81), Substance P has pro-inflammatory effects in immune and epithelial cells and participates in inflammatory diseases of the respiratory, gastrointestinal, and musculoskeletal systems.

Cell derived mediators that are released as a result of the inflammatory process then contribute to exciting group IV afferent C fibers which affect the spinal cord, as well as substance P. This substance P affects the cells, leading to the release of additional cell derived mediators. This abbreviated inflammatory cycle is neurogenic inflammation. Some of the fatty

acid-derived mediators that are pro-inflammatory include leukotriene B4 (LTB4), prostaglandin E1 (PGE2), and thromboxane A2 (TXA2). Some of the amino acid/peptide mediators that are pro-inflammatory include serotonin (5-HT), histamine, interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor (TNF), and growth factors. These fatty acid-derived and amino acid/peptide pro-inflammatory mediators are increased by several factors. These include reduced micronutrient intake of vitamins and minerals, lack of nuclear factor-kappa B (NF-kB) modulation, increased omega-6 fatty acids and reduced omega-3 fatty acids, reduced magnesium intake, reduced potassium intake, reduced phytonutrient and antioxidant intake, reduced vitamin D, and diabetes (23).

This physiology explains why an anti-inflammatory diet and key supplements are thought to help with many diseases that have their roots in inflammation, such as fibromyalgia. The main idea behind eating a low inflammatory diet is that the omega-6 to omega-3 ratio becomes more balanced, with an ideal set at no higher than 4:1, respectively. The diet consists of lean protein, such as fish, omega-3 beef, chicken, and eggs; dark chocolate; vegetables and fruits; olive oil; herbs and spices, including garlic, ginger, and turmeric; raw nuts; green tea; red wine; and stout beer. These food choices are good for disease prevention and health promotion. The key supplements include a basic daily intake of a multi-vitamin, magnesium with calcium, EPA/DHA, vitamin D, and a probiotic. The diet and supplements work to modulate inflammation within the system, thereby reducing the promotion and effects of the disease (23).

Treatment Options for Fibromyalgia

As mentioned previously, when central sensitization has occurred in chronic pain patients, little additional nociceptive input is required to maintain the sensitized state. Therefore, daily activities that seem harmless may contribute to the maintenance of chronic pain. In

addition, the dissolution of painful sensations is prolonged in patients with fibromyalgia, which results in slow reductions of their pain levels during rest as well as brief therapeutic interventions. Many frequently used analgesic medications do not improve central sensitization. In fact, there are some medications, including opioids, which have been shown to maintain or even worsen this central nervous system condition (65).

Pregabalin, also known as Lyrica, is a common drug used to treat fibromyalgia. It is a synthetic molecule and a structural derivative of the inhibitory neurotransmitter [gamma]-aminobutyric acid. It is a ligand that has analgesic, anticonvulsant, anxiolytic, and sleep-modulating activities. The pregabalin mainly binds to the [alpha]2-[delta] subunit of presynaptic, voltage-dependent calcium channels that are widely distributed throughout the peripheral and central nervous system. This results in a reduction in the release of several neurotransmitters, including glutamate, noradrenaline, serotonin, dopamine, and substance P. Up-regulation of the [alpha]2-[delta] subunit may play an important role in hypersensitization processes. Pregabalin appears to produce an inhibitory modulation of neuronal excitability, particularly in areas of the central nervous system dense in synaptic connections, such as the neocortex, amygdale, and hippocampus (82).

The efficacy and safety of pregabalin up to 450 mg/day, taking 150 mg three times a day, were evaluated for reducing pain and associated symptoms in patients with fibromyalgia. Patients were randomized to receive 150, 300, or 450 mg/day of pregabalin or placebo. Compared with those receiving placebo, patients treated with pregabalin 450 mg/day showed significant improvement in pain scores at week 1, and this was maintained throughout week 7. However, there was no statistically significant improvement from placebo at week 8. Reasons for the loss of statistically significant difference at week 8 may include reduced statistical power

at later time points or lack of durability of analgesic effect. Patients receiving 300 and 450 mg/day pregabalin also experienced reduced fatigue and improved sleep quality compared with those receiving pregabalin 150 mg/day or placebo. In addition, forty-eight patients (9%) withdrew because of adverse events, and 44 patients (8%) withdrew because of lack of efficacy. The most common adverse effects were somnolence in 29.2% and dizziness in 22.2%. Other adverse effects include dry mouth in 9.1%, peripheral edema in 6.1%, blurred vision in 6.4%, weight gain in 5.6%, and abnormal thinking in 5.4% (82).

Previous studies have suggested that there is a potential role for chiropractic care in the management of patients with fibromyalgia. One study by G. Hains and F. Hains (83) set two main objectives. First, to provide preliminary information on whether a regimen of 30 chiropractic treatments combining ischemic compression and spinal manipulation effectively reduces the intensity of pain, sleep disturbance, and fatigue associated with fibromyalgia. Secondly, to study the dose-response relationship and identify the baseline characteristics that may serve as predictors of outcome. Participating subjects were adult members of a regional Fibromyalgia Association that were greater than 18 years old, had widespread pain for greater than 3 months, and had previously been diagnosed with fibromyalgia by their family physician or rheumatologist. A minimum 50% improvement in pain intensity from baseline to the end of the treatment trial was needed to include the patient in the respondent category. Subjects were assessed with self-administered questionnaires taken at baseline, after 15 and 30 treatments, and 1 month after the end of the treatment trial.

Fifteen women with a mean age of 51.1 years completed the trial. A total of 9 or 60% of the patients were classified as respondents. A statistically significant lessening of pain intensity and corresponding improvement in quality of sleep and fatigue level were observed after 15 and

30 treatments. After 30 treatments, the respondents showed an average lessening of 77.2% with a standard deviation of 12.3% in pain intensity, an improvement of 63.5% with a standard deviation of 31.6% in sleep quality, and a decrease of 74.8% with a standard deviation of 23.1% in fatigue level. The improvement in the 3 outcome measures was maintained after 1 month without treatment. Subjects with less than 35% improvement after 15 treatments did not show a satisfactory response after 30 treatments. A trend, determined as not statistically significant, suggests that older subjects with severe and or chronic pain and a greater number of tender points respond more poorly to treatment. Two nonrespondents underwent an additional course of 30 treatments and therefore did not complete the 1 month follow-up period required for the last assessment. A total of 13 subjects completed the 1 month follow-up assessment. This study suggests that chiropractic care combining ischemic compression and spinal manipulation may help patients with fibromyalgia. A placebo-controlled randomized clinical trial is recommended to test this hypothesis (83).

Conclusion

Fibromyalgia is a chronic pain syndrome characterized by a history of widespread pain that is present in at least 11 of 18 tender point sites on digital palpation. It affects mostly women between 45 and 60 years of age. Although the exact cause of this condition is uncertain, there is increasing evidence suggesting that activation of pain receptors, transmission and modulation of pain signals, neuroplasticity, and central sensitization are all part of the inflammatory response.

Central sensitization involves the central nervous system neurons becoming hyper-excitable, leading to hyperalgesia and allodynia. This results in the type of chronic widespread pain that characterizes fibromyalgia. This sensitization can be activated by different mechanisms,

including wind-up, dysregulated descending inhibitory pathways, and upregulated facilitatory modulation.

Significant factors contributing to central sensitization, resulting in neurogenic inflammation, include, but are not limited to: substance P, nitric oxide, tumor necrosis factor (TNF), serotonin (5-HT), histamine, interleukin-1 (IL-1), interleukin-6 (IL-6), growth factors, leukotriene B4 (LTB4), prostaglandin E1 (PGE2), and thromboxane A2 (TXA2). Decreases in zinc, magnesium, and vitamin D have also been proven to show clinical correlation in patients with fibromyalgia. Based on these contributing factors, it is believed that a diet that moderates inflammation, along with key supplementation, can help patients with fibromyalgia.

Other treatment options include pharmaceuticals, with one of the most popular being Lyrica. However, it was not proven to show any lasting benefit after a couple months of use and presented with several different side effects. Chiropractic care was also suggested as a treatment method for patients. Based on preliminary research, there appears to be some lasting benefit with the use of ischemic compression and spinal manipulation.

Additional research is needed in determining the causes of fibromyalgia and effective treatment options. Over the last several years there has been an increase in the number of people diagnosed with fibromyalgia. This supports the idea that nutritional factors related to central sensitization and neurogenic inflammation play a large role in this pathology.

As a healthcare professional, it is extremely important that the mechanism which brings on this syndrome is understood. With knowledge of its' origin, treatments can be better developed and applied. In addition, patients can have a better understanding of their condition and methods available to reduce their pain. This should result in a better quality of life for these people, which is the ultimate goal in our healthcare profession.

References

1. Ablin J, Neumann L, Buskila D. Pathogenesis of fibromyalgia - A review. Joint Bone Spine 2008; 75: 273-9.

2. Abeles AM, Pillinger MH, Solitar BM, Abeles M. Narrative Review: The Pathophysiology of Fibromyalgia. Ann Intern Med 2007; 146: 726-34.

3. Seaman D, Cleveland C. Spinal Pain Syndromes: Nociceptive, Neuropathic, and Psychologic Mechanisms. J Manipulative Physiol Ther 1999; 22: 458-72.

4. Winkelstein BA. Mechanisms of central sensitization, neuroimmunology and injury biomechanics in persistent pain: implications for musculoskeletal disorders. J Electromyogr Kinesiol 2004; 14: 87-93.

5. Meeus M, Nijs J. Central sensitization: a biophysical explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. Clin Rheumatol 2007; 26: 465-73.

6. Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, Dayer P, Vischer TL. Neurophysiologic Evidence for a Central Sensitization in Patients With Fibromyalgia. Arthritis Rheum 2003; 48: 1420-9.

7. Omoigui S. The biochemical origin of pain: The origin of all pain is inflammation and the inflammatory response. Part 2 of 3 - Inflammatory profile of pain syndromes. J Me Hy 2007; 69: 1169-78.

8. Staud R, Bovee C, Robinson M, Price D. Cutaneous C-fiber pain abnormalities of fibromyalgia patients are specifically related to temporal summation. Pain 2009; 139:315-23

9. Mense S. Muscle Pain: Mechanisms and Clinical Significance. Dtsch Arztebl Int 2008; 105: 214-9.

10. Lawson, K. Treatment options and patient perspectives in the management of fibromyalgia: future trends. Neuropsychiatric Disease and Treatment 2008; 4:1059-71.

11. Schneider M, Vernon H, Ko G, Lawson G, Perera J. Chiropractic Management of Fibromyalgia Syndrome: A Systematic Review of the Literature. J Manipulative Physiol Ther 2009; 32: 25-40.

12. Schneider MJ, Brady DM, Perle SM. Commentary: Differential Diagnosis of Fibromyalgia Syndrome: Proposal of a Model and Algorithm for Patients Presenting With the Primary Symptom of Chronic Widespread Pain. J Manipulative Physiol Ther 2006; 29: 493-501.

13. Clauw DJ. The Pathogenesis of Chronic Pain and Fatigue Syndromes, with Special Reference to Fibromyalgia. Medical Hypotheses 1995; 44: 369-378.

14. Henriksson KG. Pathogenesis of Fibromyalgia. J Muscoskeletal Pain 1993; 1: 3-16.

15. Bell IR, Baldwin CM, Schwartz GE. Illness from Low Levels of Environmental Chemicals: Relevance to Chronic Fatigue Syndrome and Fibromyalgia. Am J Med 1998; 105: 74-82.

16. DeSantana JM, Sluka KA. Central Mechanisms in the Maintenance of Chronic Widespread Noninflammatory Muscle Pain. Curr Pain Headache Rep 2008; 12: 338-43.

17. Tracy RP. The Five Cardinal Signs of Inflammation: Calor, Dolor, Rubor, Tumor…and Penuria. J Gerontology 2006; 61A: 1051-1052.

18. Smith LL. Acute inflammation: the underlying mechanism in delayed onset muscle soreness? Med Sci Sports Exerc 1991: 23(5): 542-551.

19. Meggs WJ. Neurogenic Switching: A Hypothesis for a Mechanism for Shifting the Site of Inflammation in Allergy and Chemical Sensitivity. Environ Health Perspect 1995; 103(1): 54-56.

20. Foreman JC. Peptides and neurogenic inflammation. Br Med Bull 1987; 43: 386.

21. Hinsey JC, Gasser HS. The component of the dorsal root mediating vasodilation and the Sherrington contracture. Am J Physiol 1930; 92: 679.

22. Chahl LA. Antidromic vasodilation and neurogenic inflammation. Pharmacol Ther 1988; 37: 275-300.

23. Seaman D. Chiropractic Nutrition Specialist Certification Education. 2005.

24. Cavagnaro J, Lewis RM. Bidirectional regulatory circuit between the immune and neuroendocrine systems. Year Immunol 1989; 4: 241-252.

25. Onorato J, Merland N, Terral C, Michel FB, Bousquet J. Placebo-controlled double-blind food challenge in asthma. J Allergy Clin Immunol 1986; 78: 1139-1146.

26. Bousquet J, Chanez P, Michel F-B. The respiratory tract and food hypersensitivity. In: Food allergy: adverse reactions to foods and food additives (Mercalfe DD, Sampson HA, Simon RA, eds). Oxford: Blackwell Scientific Publications 1991; 139-149.

27. Adkins FM. Food-induced urticaria. In: Food allergy: adverse reactions to foods and food additives (Metcalfe DD, Sampson HA, Simon RA, eds). Oxford: Blackwell Scientific Publications 1991; 129-138.

28. Parke AI, Hughes GRV. Rheumatoid arthritis and food: a case study. Br Med J 1981; 282: 2027-2029.

29. Panush RS, Stroud RM, Webster EM. Food induced (allergic) arthritis: clinical and serological studies. Arthritis Rheum 1986; 29: 220.

30. Egger J, Wilson J, Carter CM, Turner MW. Is migraine food allergy? A double-blind trial of oligoantigenic diet treatment. Lancet 2 1983; 865-869.

31. Mansfield LE, Vaughan TR, Waller SF, Haverly RW, Ting S. Food allergy and adult migraine: double-blind and mediator confirmation of an allergic etiology. Ann Allergy 1985; 55: 126-129.

32. Randolph TG. Human ecology and susceptibility to the chemical environment. Springfield, IL-C. C Thomas; 1962.

33. Tabershaw IR, Cooper WC. Sequelae of acute organic phosphate poisoning. J Occup Med 1966; 8: 5-19.

34. Cullen MR. The worker with chemical sensitivities: an overview. State Art Rev Occup Med 1987; 2: 655-661.

35. Meggs WJ. Neurogenic inflammation and sensitivity to environment chemicals. Environ Health Perspect 1993; 101: 234-238.

36. Gronblad M, Konttinen YT, Korkala O, Liesi P, Hukkanen M, Polak JM. Neuropeptides in synovium of patients with rheumatoid arthritis and osteoarthritis. J Rheum 1988; 15: 1807-1810.

37. Silberstein SD. Advances in understanding the pathophysiology of headache. Neurology 1992; 42(2): 6-10.

38. Buzzi MG, Moskowitz MA. The trigemino-vascular system and migraine. Pathol Biol 1992; 40: 313-317.

39. Zimerman M. Pathophysiologic mechanisms of fibromyalgia. Clin J Pain 1991; 7: S8-15.

40. Merskey H, Bogduk N. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms, 2nd ed. IASP, Seattle 1994.

41. Staud R. Evidence of involvement of central neural mechanisms in generating FM pain. Curr Rheumatol Rep 2002; 4: 299-305.

42. Staud R, Smitherman ML. Peripheral and central sensitization in FM: pathogenic role. Curr Pain Headache Rep 2002; 6: 259-266.

43. Eriksen HR, Ursin H. Subjective health complaints, sensitization, and sustained cognitive activation (stress). J Psychosom Res 2004; 56: 445-448.

44. Baranauskas G, Nistri A. Sensitization of pain pathways in the spinal cord: cellular mechanisms. Prog Neurobiol 1998; 54: 349-365.

45. DeLeo JA, Windelstein BA. Physiology of chronic spinal pain syndromes: from animal models to biomechanics. Spine 2002; 27: 2526-2537.

46. Li J, Simone DA, Larson AA. Windup leads to characteristics of central sensitization. Pain 1999; 79: 75-82.

47. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain 1993; 52: 259-285.

48. Graven-Nielsen T, Arendt-Nielsen L. Peripheral and central sensitization in musculoskeletal pain disorders: an experimental approach. Curr Rheumatol Rep 2002; 4: 313-321.

49. Kidd BL, Urban LA. Mechanisms of inflammatory pain. Br J Anaesth 2001; 87: 3-11.

50. Gracely RH, Grant MA, Giesecke T. Evoked pain measures in fibromyalgia. Best Pract Res Clin Rheumatol 2003; 17: 593-609.

51. Bennett GJ. Update on the neurophysiology of pain transmission and modulation: focus on the NMDA-receptor. J Pain Symptom Manage 2000; 19: S2-S6.

52. Meller ST, Gebhart GF. Nitric oxide (NO) and nociceptive processing in the spinal cord. Pain 1993; 52: 127-136.

53. Luo ZD, Cizkova D. The role of nitric oxide in nociception. Curr Rev Pain 2000; 4: 459-466.

54. Liu H, Brown JL, Jasmin L, Maggio JE, Vigna SR, Mantyh PW, Basbaum AI. Synaptic relationship between substance P and the substance P receptor: light and electron microscopic characterization of the mismatch between neuropeptides and their receptors. Proc Natl Acad Sci USA 1994; 91: 1009-1013.

55. Dubner R, Ken K. Endogenous mechanisms of sensory modulation. Pain Suppl 1999; 6:S45-53.

56. Wei F, Dubner R, Ren K. Dorsolateral funiculus-lesions unmask inhibitory or disfacilitatory mechanisms which modulate the effects of innocuous mechanical stimulation on spinal Fos expression after inflammation. Brain Res 1999; 820: 112-116.

57. Ren K, Dubner R. Enhanced descending modulation of nociception in rats with persistent hindpaw inflammation. J Neurophysiol 1996; 76: 3025-3037.

58. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000; 288: 1765-1769.

59. Le Bars D, Villaneuva L. Electrophysiological evidence for the activation of descending inhibitory controls by nociceptive afferent pathways. Prog Brain Res 1988; 77: 275-299.

60. Zusman M. Forebrain-mediated sensitization of central pain pathways: 'non-specific' pain and a new image for MT. Man Ther 2002; 7: 80-88.

61. Rygh LJ, Tjolsen A, Hole K, Svendsen F. Cellular memory in spinal nociceptive circuitry. Scand J Psychol 2002; 43: 153-159.

62. Inanici F, Yunus MB. History of fibromyalgia: past to present. Curr Pain Headache Rep 2004; 8(5): 369-378.

63. Lawson K. Treatment options and patient perspectives in the management of fibromyalgia: future trends. Neuropsych Dis Treat 2008; 4(6): 1059-1071.

64. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. Arthritis Rheum 1990; 33: 160-72

65. Staud R, Spaeth M. Psychophysical and Neurochemical Abnormalities of Pain Processing in Fibromyalgia. CNS Spectr 2008; 13(3) (suppl 5): 12-17.

66. Russell IJ, Orr MD, Littman B, et al. Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. Arthritis Rheum 1994; 37(11): 1593-1601.

67. Bradley LA, Sotolongo A, Alberts KR, et al. Abnormal regional cerebral blood flow in the caudate nucleus among fibromyalgia patients and non-patients is associated with insidious symptom onset. J Musculoskelet Pain 1999; 7: 285-292.

68. Larson AA, Giovengo SL, Russell IJ, Mechalek JE. Changes in the concentrations of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: implications for nitric oxide pathways. Pain 2000; 87(2): 201-211.

69. Giovengo SL, Russell IJ, Larson AA. Increased concentrations of nerve growth factor in cerebrospinal fluid of patients with fibromyalgia. J Rheumatol 1999; 26(7): 1564-1569.

70. Crofford LJ, Young EA, Engleberg NC, et al. Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. Brain Behav Immun 2004; 18(4): 314-325.

71. Crofford LJ. The hypothalamic-pituitary-adrenal axis in fibromyalgia: Where are we in 2001? J Musculoskelet Pain 2002; 10: 215-220.

72. Murphy RM, Zemlan FP. Differential effects of substance P on serotonin-modulated spinal nociceptive reflexes. Psychopharmacol (Berl) 1987; 93(1): 118-121.

73. Giovengo SL, Russell IJ, Larson AA. Increased concentrations of nerve growth factor in cerebrospinal fluid of patients with fibromyalgia. J Rheumatol 1999; 26(7): 1564-1569.

74. Watkins LR, Milligan ED, Maier SF. Glial activation: a driving force for pathological pain. Trends Neurosci 2001; 24(8): 450-455.

75. Wieseler-Frank J, Maier SF, Watkins LR. Glial activation and pathological pain. Neurochem Int 2004; 45: 389-395.

76. Wieseler-Frank J, Maier SF, Watkins LR. Central proinflammatory cytokines and pain enhancement. Neurosignals 2005; 14(4)166-174.

77. Watkins LR, Maier SF. When good pain turns bad. Curr Dir Psychol Sci 2003; 12(6): 232-236.

78. Sendur OF, Tastaban E, Turan Y, Ulman C. The relationship between serum trace element levels and clinical parameters in patients with fibromyalgia. Rheumatol Int 2008; 28(11): 1117-21.

79. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004; 80(suppl): 1678S-88S.

80. Shaheen AB, Niaz AS, Muhammad I, Syed MK, Aneel SV, Aneel S, Gunpat. Vitamin D deficiency in Fibromyalgia. JPMA 2010; 60; 949.

81. O'Connor TM et al. The role of substance P in inflammatory disease. J Cellular Physiol 2004; 201:167-80.

82. Gajraj NM. Pregabalin: its pharmacology and use in pain management. Anesth Analg 2007; 105: 1805-15.

83. Hains G, Hains F. Combined Ischemic Compression and Spinal Manipulation in the Treatment of Fibromyalgia: A Preliminary Estimate of Dose and Efficacy. J Manipulative Physiol Ther 2000; 23: 225-30.