

LITERATURE REVIEW

# HISTOLOGY AND BIOCHEMICAL MILIEU OF TRIGGER POINTS: A LITERATURE REVIEW

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## ABSTRACT

**Introduction:** Myofascial Trigger Points (MTrPs) are one of the common causes of musculoskeletal pain. Many of people are suffer pain of this syndrome. This syndrome is a complex process that involves the interaction of biochemical factors, histological change, nociceptors and the neurons of both the central and peripheral nervous systems. Recent studies of MTrPs have focused on the role of biochemical markers such as neuropeptides and inflammatory mediators, etc. Our main aim in the present article was to review studies regarding the biochemical and histological changes related to myofascial pain.

**Method:** A comprehensive search was performed of databases Science Direct, Google Scholar and PubMed using OR AND between the selected keywords: myofascial pain, MTrP, prostaglandins, calcitonin gene related peptide, tumor necrosis factor, inflammation mediators and microdialysis in articles published between 1996 to 2016.

**Result:** Eighty-five articles were initially obtained from the search of the electronic sources. Sixteen articles were selected after reading and classifying materials and articles based on the inclusion criteria.

**Conclusion:** The process of inflammation and its involvement in muscle pain and cytokines secreted by inflammatory cells and muscle tissue leads to increased inflammation and pain. Interaction among mediators, muscle tissue and neurons of the spinal cord lead to persistent pain and change pain type. This pathophysiologic process in trigger points may suggest useful and effective ways of providing better treatment for people experiencing myofascial pain.

**Keywords:** Trigger Point; Muscle Pain; Biochemical Marker; Inflammatory Mediator; Microdialysis; MTrP.

## INTRODUCTION

Musculoskeletal pain is one of the most common reasons for referring people to pain clinics and treatment centers around the world. One-third of patients referred to clinics suffer from myofascial pain syndrome with myofascial trigger points (MTrPs). In an American, 30-80 percent of patients referred to every pain clinic have had MTrPs. A study showed that MTrP is the primary cause of pain in 85-95 percent of people referred to clinics. In another study, 55% of the 164 referred patients with chronic neck pain and headache had active MTrPs [1, 2].

The muscle fibers and nerve components of MTrPs have involved, lead to increase pain intensity, referred pain and activity change of motor and may cause many problems like hyperalgesia, radicular pain, limitation of motion, joint stiffness and muscle weakness. Furthermore, in visceral pain, headache, dizziness, nausea, insomnia, skin discoloration, and involvement of the sympathetic nervous

system have been reported as side effects of MTrP [3, 4]. These diseases have a significant impact on the quality of life in the patient and impose a heavy financial burden on the health systems.

MTrPs are caused following a trauma, overuse, frequent muscle contractions, wrong postures and stress (3). MTrPs with structural and biochemical changes in a tissue cause severe radicular pain, limitation of motion, joint stiffness and impaired proprioception [2, 4, 5]. The aim of this literature review is to discuss the histology and biochemical changes of MTrPs in muscle tissue.

### Diagnosis of MTrP

MTrPs are diagnosed based on clinical history, physical examination and palpation of muscles. Four criteria have been used for diagnosis [1, 4, 5]:

1. Palpable taut band on the involved muscle.
2. Sometime muscles experience local twitches by pres-

sure.

3. Feeling of a sharp pain by pressing. Sometimes, the pain is referred to somewhere else.
4. Decreased range of motion of the related joint.

### MTrP mechanism

Although the etiology of MTrP is not fully understood, there is general agreement that factors such as overuse of muscle or direct trauma to the muscle and subsequently hypoxia and cell injury. Overuse syndrome is one of the causes of MTrPs, which continuous and sequential contractions in a muscle leads to this type of damage. One study showed that changes in blood pressure during contraction of the muscle in arterial blood pressure is and venous blood pressure is 35 mmHg and 15 mmHg, respectively. This pressure difference consequently leads to muscle blood drainage. In normal muscle at rest and with the expansion of the muscle, blood arrives at the muscle and provides the context for normal metabolism. But, in frequent contractions after taking ATP and CP, the muscle enters the anaerobic stage that leads to the production of pyruvic acid. This causes a decrease in muscle tissue pH. Increase of the concentration of hydrogen ions in muscle tissue causes cell damage. Damage to muscle tissue activates the inflammation phenomenon [3, 6, 7]. Given the above, one of the causes of trigger points in muscles is a impaired of blood circulation in the muscle. Using Doppler sonography, Approved that there is a significant difference between blood circulation in a healthy muscle and a muscle with MTrPs [8].

### Inflammatory phase of MTrP

The process of MTrP inflammation is like other parts of the body. The process contains two phases. The first phase includes primary injury, which usually follows an external factor (like overuse syndrome) leading to cell damage and production of substances known as inflammation chemical mediators. Secondary injury is caused through activity of the inflammatory mediators, which is more significant than the primary injury. This causes pain, added damage and histological and biochemical changes. The substances include histamine, serotonin, proteins of the complement system, bradykinin, prostaglandins, calcitonin gene-related protein, substance P, cytokines including IL<sub>6</sub>, TNF, etc. Nociceptor stimulations in local MTrP transmit impulses to the spinal cord. Continuous stimulation of nociceptors leads to secretion of inflammatory mediators neuronal cell body of the dorsal horn. This phenomenon is called neurogenic inflammation [9, 10].

Stimulation of other neurons in the dorsal horn of the spinal cord via the neural network elicits referral pain and local twitch response due to existent connections among them. Complex interaction of MTrP, inflammatory mediators and the nervous system leads to severe pain, increased symptoms of MTrP, subsequent change of MTrP histology and MTrP chemical milieu [10, 11]. This is an important challenge for researchers of myofascial pain; therefore, we conducted this review article to describe the histology and biochemical milieu of MTrPs. We summarized the findings

about morphology and histology (Table 1) and biochemical markers (Table 2) of MTrPs considering the subject types (animal/human), the interventions used and the results found.

**Table 1:** Studies of morphology and histology of MTrP

No.	Ref. No.	Author	Year	Subject	Intervention	Result
1	13	Simons et al.	1976	Dog	Histological study of palpable hardening band of gracilis and semitendinosus muscles of dogs were compared with the histological findings reported in painful spots and muscle hardenings of human muscles.	Longitudinal sections revealed densely stained fibers with conspicuous bulges of dog muscle that they referred to as 'contraction knots'.
2	14	Windisch et al.	1999	Human	Selected biopsies as well as larger tissue samples were taken from 11 corpses and were subsequently prepared for histological study.	A histologically constant, significant morphological alteration was found in the areas of concern. The spaces between the individual muscle fibers of healthy muscle tissue appear relatively wide, the endomysium of the myogelotic area are clearly narrowed.
3	15	Mense et al.	2003	Rat	To test this hypothesis in rats; In the skeletal muscle, a local increase of acetylcholine (ACh) in a few end plates has been hypothesized to cause the formation of contraction knots that can be found in MTrPs.	The results support the assumption that a dysfunctional end plate exhibiting increased release of ACh may be the starting point for regional abnormal contractions, which are thought to be essential for the formation of MTrPs.
4	16	Hsieh et al.	2012	Rabbit	Histopathological Evaluation of the muscles with a Taut Band and a Nontaut Band. In the histomorphometric analysis by H&E staining, the nontaut band portion of the biceps femoris muscle showed a skeletal muscles with normal morphology the MTrPs of a skeletal muscle in rabbit.	The endomysium enveloping each muscle fiber in the taut band of the biceps femoris was narrow and cramped, suggesting an enlargement of muscle fibers due to shortening and tightness of the contractile unit or focal muscle edema.
5	17	Akamatsu et al.	2014	Human	To study anatomical correlations between the accessory nerve branches entering the muscle belly to reach the motor endplates and MTrPs on both trapezius muscles from twelve adult cadavers.	Seven points are described, four of which are motor points. In all cases, these locations corresponded to clinically described MTrPs. The four points were common in these twelve cadavers.

**Table 2: Studies of biochemical MTrP**

No.	Ref. No.	Author	Year	Subject	Intervention	Result
1	6	Issberner et al.	1996	Human	They used submaximal effort tourniquet technique' and, in a second attempt, an intramuscular pressure infusion of acid phosphate buffer and measured pH and deep muscular pain	The muscular pain induced by infusion of acidic phosphate buffer and pain from ischemic contractions are generated through the same mechanisms based on the algogenic action of protons.
2	18	Schäfers et al.	2003	Rat	TNF, exogenous formalin (9%) or vehicle was injected into the gastrocnemius or biceps brachii muscles of rats.	Proinflammatory cytokines (TNF $\alpha$ ) might be beneficial for the treatment of musculoskeletal pain syndromes.
3	19	Rosendal et al.	2005	Human	Interstitial concentrations of potassium K <sup>+</sup> lactate dehydrogenase (LDH), interleukin-6 (IL-6) and collagen turnover determined in the trapezius muscle by the microdialysis technique.	Patients with chronic pain in the trapezius muscle had increased levels of interstitial potassium. This finding could be causally related to myalgia or secondary to pain due to deconditioned muscle or altered muscle activity pattern.
4	5	Shah et al.	2005	Human	They used in vivo micro analytical techniques for measuring biochemicals in the human muscle.	The biochemical milieu were igher than in MTrP such as H <sup>+</sup> , bradykinin, calcitonin gene-related peptide, substance P, tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , serotonin and norepinephrine.
5	20	Jonhagen et al.	2006	Human	To detect neuropeptides in human skeletal muscle at rest and after eccentric exercise.	High levels of CGRP after heavy eccentric exercise may be associated with the regulation of delayed onset muscle soreness and possibly also the stimulation of tissue regeneration.
6	21	Shah et al.	2008	Human	They used in vivo micro analytical techniques for measuring biochemicals in the human muscle with MTrP and normal muscle.	The concentration of biochemicals were higher in muscles with MTrP then normal muscle biochemical marker such as bradykinin, substance P, calcitonin gene-related peptide, tumor necrosis factor alpha, interleukin 1 <sub>(IL-1)</sub> , IL-6, etc.
7	16	Hsieh et al.	2012	Rabbit	They investigated the activities of $\beta$ -endorphin, substance P, TNF- $\alpha$ , COX-2, HIF-1 $\alpha$ , iNOS and VEGF after different dosages of dry needling at the myofascial trigger spots of a skeletal muscle in rabbits.	After 1D treatment enhanced the $\beta$ -endorphin levels in the biceps femoris and serum and reduced substance P in the biceps femoris and DRG; 5D treatment reversed these effects and was accompanied by increase of TNF- $\alpha$ , COX-2, HIF-1 $\alpha$ , iNOS and VEGF production in the biceps femoris.

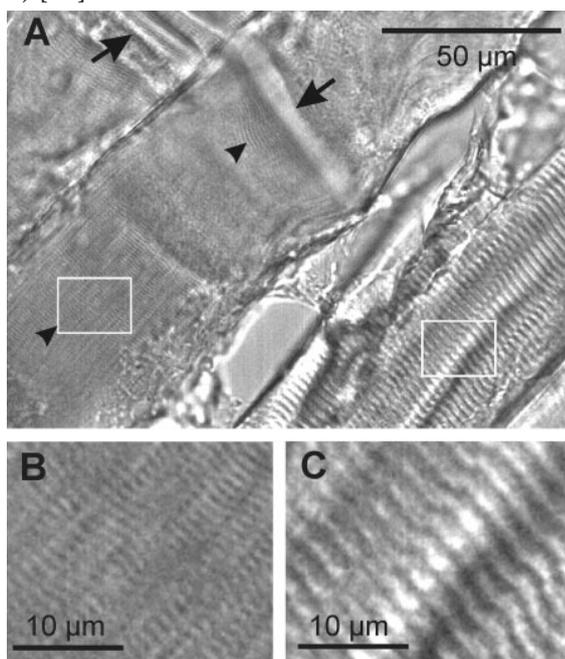
8	24	Moras-ka et al.	2013	Human	They studied changes in blood flow and cellular metabolism at myofascial trigger points after ischemic compression.	Following intervention, increased concentration of lactate and glucose also increased blood flow were observed.
9	25	Hsieh et al.	2014	Rabbit	Their study evaluated the remote effects of dry needling with different dosages on the expressions of substance P (SP) in the proximal muscle and spinal dorsal horns of rabbits.	Immediately after dry needling for 1D and 5D, the expressions of SP were significantly decreased in ipsilateral Biceps femoris and bilateral spinal superficial laminae, but decreased in the 5D group after five days.
10	26	Hsieh et al.	2015	Rabbit	They used low power laser as physical treatment on MTrP, then measured levels of biomarkers.	TNF and COX2 reduced in muscle tissue and SP decreased in DRG; also, $\beta$ -ep increased into serum.
11	23	Grosman et al.	2016	Human	They studied biomarkers and some growth factors of blood in experimental group=37 and control group=21.	Cytokines such as IL-6, TNF, IL-12, MCP-1, MDC, GM-CSF, IL-8, MIP-1b, FGF-2, PDGF and VEGF were higher in the experimental group than the control group.

### Histology of MTrP

One of the symptoms of MTrP is a tight band of muscle fibers. MTrPs are small areas with damaged muscle tissue. Biopsy of these points of living muscles is difficult and is often associated with tissue destruction and artifacts. Despite these difficulties, in this regard, several studies have been conducted some of which are presented as follows:

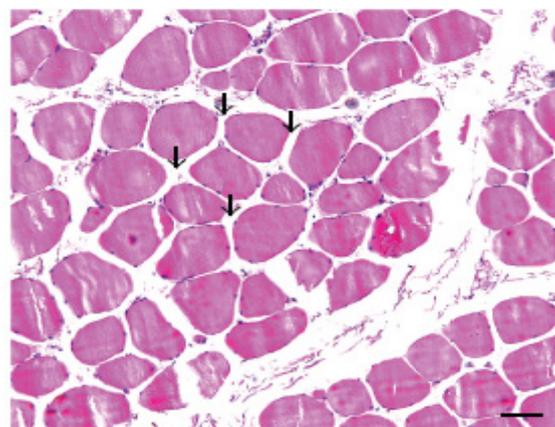
Glogowski and Wallraff (1951) reported swollen and club like points in muscle tissue of patients with muscle pain similar to painful points of patients with fibromyalgia syndrome. In that time, several terms were used to describe muscle pain, among them myalgic spots, fibrositis and myogeloses [12]. Histological changes were considered by researchers, and one of these people was Simons et al. (1976) which sampled parts of a dog's muscle with a tight band (based on clinical findings, it is in accordance with the MTrPs) under anesthesia. After sample preparation and microscopic investigation, they declared that those points are contraction knots of the muscle [13]. Windisch et al. (1999) studied muscle tissue samples taken from fresh 11 cadavers. They selected biopsies from tight bands of muscles and then prepared for histological study. Significant morphological changes were found in each sample. In healthy muscle tissue, spaces of inter muscle fibers (endomysium) were wide, but in the sample of tight band inter muscle fiber, the observed spaces were narrow. In their electron microscopy study, they found the diameter of A bands larger than normal and the diameter of I bands narrower than normal condition, which indicates local contraction [14]. A study by Mense et al. (2003) has shown that histological changes in location of MTrPs. They tested the hypothesis that a high concentration of acetylcholine (Ach) in end plates leads to contraction knots or same MTrPs. They injected Diisopropyl fluorophosphate

(DFP) into the lower part of the gastrocnemius muscle of rats and then applied continuous electrical stimulation for 30 to 60 minutes, DFP injection led to inhibition of acetylcholinesterase and caused abnormal contraction points in same parts of the muscle compared to the muscle that was not injected. Histological sections from upper (unblocked) and lower parts of the muscle were studied by EM, showed that, these changes include contraction disks in muscle fiber that have abnormality contracted their sarcomeres. Thus, the researchers confirmed the hypothesis that a high concentration of acetylcholine in a muscle causes MTrPs (Fig. 1) [15].

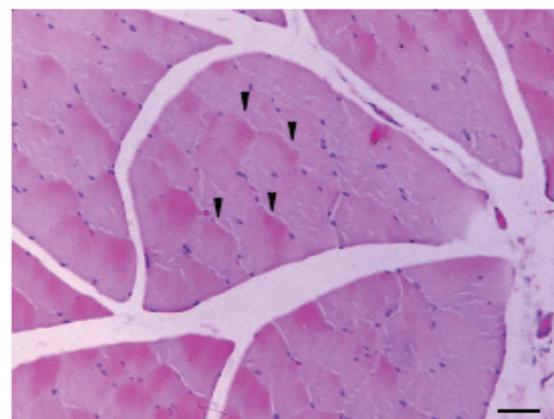


**Fig. 1.** Contraction-disk complexes (injection of 1 M DFP, electrical stimulation for 6 min at 1 Hz). A: 2 muscle fibers crossing the upper left of the figure show multiple contraction disks whose centers appear as white bands without any discernible structures (arrows). Areas with abnormally contracted sarcomeres are marked with arrowheads. The fiber to the lower right shows undisturbed sarcomere. From Mense et al. (2003, *Journal of Applied Physiology* 94: 2494–2501), with permission. B: left boxed area in A at a higher magnification to show the abnormally contracted sarcomeres. C: right boxed area in A exhibiting normal A band spacing.

In this area, Hsieh et al. (2012) examined trigger point's morphology and compared it with healthy muscle tissue in rabbit biceps femoris. They took a sample from the tightened muscle and normal band area. After processing of tissue sections and staining by H&E, the sample was compared with healthy muscle samples by light microscopy. In healthy muscles, polygonal muscle fibers with multi-nuclei are located inside the endomysium and endomysium space is clearly marked; however, in the muscle with MTrPs, muscle fibers were enlarged and endomysium space was narrow suggesting enlargement of muscle fibers was caused due to edema in this area by inflammation phenomena. They interpreted these points as location of the contracted sarcomere (Fig. 2)[16].



(a)



(b)

**Fig. 2:** Morphological findings of representative skeletal muscles with nontaut and taut bands. (a) Biceps femoris with a nontaut band; (b) Biceps femoris with a taut band (H&E staining, scale bar = 5 µm).

From Yueh-ling Hsieh and et al.: *Hindawi Publishing Corporation, Evidence-Based Complementary and Alternative Medicine Volume 2012, Article ID 342165, 12 pages, with permission.*

Regarding the role of continuous nervous stimulation of muscles in creating MTrP, A group of medical Anatomists of Medicine of the University of Sao Paulo (FMUSP) studied relationship between nerves and muscle fibers. They (2014) carefully dissected 12 adult bodies (6 men and 6 women) whereby exact checking of bilateral trapezius muscles of the corpses identified the site where the accessory nerve branches enter the muscle. They found that in site the motor nerves link, many of locations correlated to clinically described MTrPs. The correlation between the eleventh nerve of the brain and muscular MTrPs can help researchers to understand the pathophysiology of MTrPs[17].

#### Biochemical milieu of MTrP

As mentioned above, the pathophysiology of muscle trigger points is still not well understood. Biochemical molecules are involved in neurogenic inflammation phenomenon. These topics are challenging issues among experts. Some of these studies are presented in the following:

Issberner et al. (1996) determined the role of hydrogen ion in ischemic muscle pain. For this purpose, they used SET (Submaximal Effort Tourniquet) technique of forearm

flexor muscles for Group 1 and injected acid phosphate buffer into forearm flexor muscles of Group 2. Then they measured skin pH in the palmar forearm directly over the forearm flexor muscle. In Group 1, with the starting of muscle contractions, hydrogen ions increased (pH value decreased), which caused muscle pain. In Group 2, muscle pain initiated after injection due to decreased pH. When normal blood circulation returned in both groups, the concentration of hydrogen ion reduced, and consequently, the pain also decreased [6].

Researchers of the US Health Organization found that pH changes in the active MTrP region and lower than normal modes. This is due to sustained contractions that cause ischemic state that lead to reduction of pH. Increase of H<sup>+</sup> concentration results in cell injury and inflammation. In addition, decrease of low level of pH for a long time reduces activity of the acetylcholinesterase enzyme and potential of the end plate remains depolarized, thus leading to contraction of the sarcomere and excite muscle nociceptors. This process leads to release calcitonin gene-related protein (CGRP) and other biochemical substance from MTrP cells. The release of these substances stimulates alpha-motor neurons and can enhance the release of acetylcholine. The above processes create a impaired cycle causing continuity of muscle contraction [3].

Mense et al. (2001) in a series of studies on musculoskeletal pain have reported that deforming the axonal membrane or chemical activation can activate nociceptors of muscle and lead to change in sensitivity muscle nociceptors also secrete endogenous biochemical Substances such as bradykinin (BK), prostaglandins(PG) and serotonin(5-HT). These substances are not only involved in the increased sensitivity of muscle nociceptors, but also produce vasodilation and plasma extravasation in the area. The resulted swelling stimulates the mechanoreceptors and disrupts the muscle nociceptor endings that secrete neuropeptides such as substance P and calcitonin gene-related peptide (CGRP), In addition, an adequate secretion of neuropeptides leads to secretion of substances such as histamine by mast cells, bradykinin by kalidin, serotonin by platelets and prostaglandins by endothelial cells. They considered an active role for muscle nociceptors in maintaining muscles' normal homeostasis [18].

The role of TNF in the process of creating MTrP was studied by Schafers et al. (2003). They injected exogenous TNF(0.1-10µg) and formalin (%9) into the gastrocnemius or biceps brachii muscles of rats. To measure muscle hyperalgesia, changes of muscle strength of fore and hind limbs were measured. Formalin made sever muscle tissue damage, TNF did not induced either tissue damage or motor dysfunction, Also Immunohistochemistry techniques were tested a day after the injection to study the effect of TNF and formalin on other inflammatory mediators such as calcium gene-related protein, prostaglandin E2 and nerve growth factor. TNF and formalin lead to increase CGRP and NGF, whereas PGE2 was increased exclusively after TNF injection. Therefore, they suggested that TNF

could be effective in improving muscle damage and also be used for treatment of musculoskeletal pain syndrome[19]. Rosendale et al. (2005) studied the biochemistry of muscle tissue before and after 20 minute activities with submaximal effort. They measured the interstitial concentration of K<sup>+</sup>, IL-6 and lactate dehydrogenase (LDH) in the experimental(female patients with chronic trapezius myalgia) and control group(healthy females) by the microdialysis technique. At all times during the experiment, K<sup>+</sup> levels of the experimental group were higher than the control group, but, the increased concentrations of IL-6, LDH were almost identical, and 20 minutes after the test, Concentration of IL-6, LDH returned to the basic level in each group. But, the concentration of potassium was still high. They suggested that increased potassium concentrations may be related to myalgia or secondary to the pain or changing muscle activity patterns[20].

A study by Jonhagen S. et al. (2006) has shown that CGRP has rolled on regeneration of muscle damage. They measured concentrations of CGRP in the quadriceps of eight healthy athletes before and after heavy eccentric exercise. Increase of CGRP was reported two days after the test. This may be associated with intensified pain, as well as, this molecule may be related with delayed muscle soreness onset and possibly is linked to stimulation of tissue regeneration[21].

Shah and a group of scientists at the America Health Research Center (2005) designed a project to study MTrPs biochemical milieu. They measured concentrations of protons, bradykinin, calcitonin gene-related peptide, substance P, TNF $\alpha$ , IL $_{1\beta}$ , serotonin and norepinephrine in the upper trapezius muscle of three groups, active MTrPs with neck pain, latent MTrPs without neck pain, and normal group. Results showed that the level of substances including hydrogen ions (decrease in pH), substance P, CGRP, bradykinin, serotonin, norepinephrine and TNF $\alpha$ , IL $_{1\beta}$  were higher in the compared to the second and third group, respectively [5].

In order to confirm and complete the above projects Shah et al. (2008) designed a new project. They used capillary electro-chromatography and immuno-capillary electrophoresis techniques in their research and compared chemical milieu of upper trapezius and gastrocnemius muscles in three groups of volunteers (nine persons): active MTrPs in upper trapezius (latent MTrPs in upper trapezius muscle) and the normal group (no neck pain no MTrPs upper trapezius muscle) all exhibited normal gastrocnemius. Results showed that concentrations of hydrogen ion, substance P, CGRP, bradykinin, serotonin, norepinephrine, TNF $\alpha$  and IL $_{1\beta}$  in the first group were higher than the two other groups, and the same results held for gastrocnemius muscle. Thus, the results obtained in 2005 were confirmed [22]. In this area, Grosman et al. (2016) studied levels of circulation inflammatory biomarkers and the growth factors in acute myofascial pain syndrome (MPS). They compared cytokines of blood in patients (n=37) with MPS and non-MPS controls (n=21). The biomarkers include

IL-6, TNF, IL-12, the chemokine, monocyte chemoattractant protein-1 (MCP-1), macrophage-derived chemokine (MDC), granulocyte macrophage colony-stimulating factor (GM-CSF), IL-8 and macrophage inflammatory proteins-1b (MIP-1b). They were significantly higher in patients with MPS than controls. This difference also existed for growth factors FGF-2, PDGF and VEGF. They suggested that inflammatory cytokines and growth factors may play an influencing role in treatment of MPS [23].

#### AFTER TREATMENT

The role of biomarkers on musculoskeletal pain elicited the question “what are the post-treatment changes of cytokines?”

In agreement with this, Moraska et al. (2013) studied the metabolism of muscle cells in MTrP undergoing ischemic compression. On two subjects with headaches caused by MTrP in the upper trapezius muscle, they measured concentration levels of acid lactate and glucose and local blood flow before and after the intervention. Concentration of glucose and lactate increased for both subjects, but increase of concentration of glucose was less for Subject 1. Blood flow was measured in based on change of ethanol outflow –to—inflow ratio that showed an increase in blood flow [24]. Hsieh et al. (2014) evaluated the effect of dry needles on MTrPs in the area of remote conducted DN on MTrPs of gastrocnemius of rabbits (New Zealand rabbits) in two groups of once DN and five times DN (5DN). Then sampled bilateral biceps femoris (proximal muscles) and spinal cord segments of L5-S2, T2-T5 and C2-C5 of both groups. Immediately after DN, values of P substance was measured in the remote muscle and in the spinal dorsal horn. In both groups, the expression of substance P significantly decreased ipsilaterally in biceps femoris and bilaterally in the spinal cord segments; however, measurement of SP five days after DN was only observed in the 5DN group. The researchers also measured levels of other cytokines related to inflammation and pain in the blood serum, muscle tissue and spinal dorsal horn. These factors include  $\beta$ -endorphin, TNF $\alpha$ , COX<sub>2</sub>, HIF<sub>1- $\alpha$</sub>  and VEGF. In Group DN1, the level of  $\beta$ -endorphin increased in muscle tissue and blood serum immediately after DN, but in Group DN5, these effects reversed by increasing levels of TNF $\alpha$ , COX<sub>2</sub> and HIF1- $\alpha$ . In addition, the levels of these biochemical factors were maintained for five days after treatment. Therefore, DN for MTrP leads to changes in biomarker levels and this depends on the DN dose [25]. In this area, They (2015) investigated the effect of low-level laser on MTrP (as a physical modality) and biochemical changes of MTrP milieu. Rabbit muscle with MTrPs was laser irradiated for five days (one session per day). Then they measured the levels of  $\beta$ -endorphin ( $\beta$ -ep), substance P (SP), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and cyclooxygenase-2 (COX-2) in biceps femoris, dorsal root ganglion (DRG) and serum. Finally, they reported that laser irradiation led to reduction of the levels of COX-2 and TNF- $\alpha$  in the muscle and SP in dorsal root ganglion and also elevated the levels of  $\beta$ -ep in serum, DRG and muscle [26].

#### CONCLUSION

Understanding changes in the biochemical environment around MTrPs explains the pathogenesis, survival and amplification of myofascial pain. Production of inflammatory mediators in the muscle and their effect on the spinal cord elucidate persistence and amplification of pain. Transmission of pain to other parts of the body can be explained by stimulation of neurons in segments up and down via neuron connections. Recently new researches in using inflammatory mediators for treatment of MTrP is underway. On the other hand, investigations have been conducted on the therapeutic methods of MTrPs that can modulate biochemical mediators associated with pain and inflammation. These studies could lead to the development of new therapeutic strategies to treat myofascial pain.

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