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Fibromyalgia syndrome and Temporomandibular disorders with muscular pain. A review.

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Abstract:	Objectives: Temporomandibular disorders (TMD) refer to a group of clinical picture affecting the masticatory muscles and temporomandibular joint that are characterized by muscular or joint pain, dysfunction (limited or altered functions) and joint noises, as well as other associated symptoms, such as tension headaches, otalgia, dizziness, tinnitus and others. Fibromyalgia (FM) is a syndrome of unknown etiology involving generalized chronic pain accompanied, in a high percentage of cases, by other symptoms such as asthenia, anxiety, depression, sleep disturbances and other less frequent symptoms, such as temporomandibular disorders (TMD). Data: data were compiled by two experienced examiners following a specific form. Sources: An electronic search was carried out in the Cochrane Central Register of Controlled Trials (CENTRAL), PUBMED, and SCOPUS electronic databases (up to April 2016, unrestricted by date or language) Study selection: comparative clinical studies with patients with both clinical pictures involving the study of pathogenic processes. Conclusions: Fibromyalgia and temporomandibular disorders with muscle pain both have profiles that affect the muscular system and therefore share many epidemiological, clinical and physiopathological symptoms. Because of this, we are led to think that there is, if not a common etiology, at least a common pathogenesis. This article revises the physiopathological processes of both clinical pictures in an attempt to determine their similarities and likenesses. This would undoubtedly help in providing a better therapeutic approach. Key Words: Temporomandibular Disorders. Fibromyalgia. Orofacial Pain. Pathogenesis
Response to Reviewers:	Dear Reviewers, the article about research progress of pathogenesis of chronic pain and neuroinflammation (Ru-Rong X et al, 2014) has been added to the references list (indicated in red), as suggested.

	Thank you very much for your work. Sincerely, Ana M. Moreno-Fernández

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Abstract

Objectives: Temporomandibular disorders (TMD) refer to a group of clinical picture affecting the masticatory muscles and temporomandibular joint that are characterized by muscular or joint pain, dysfunction (limited or altered functions) and joint noises, as well as other associated symptoms, such as tension headaches, otalgia, dizziness, tinnitus and others. Fibromyalgia (FM) is a syndrome of unknown etiology involving generalized chronic pain accompanied, in a high percentage of cases, by other symptoms such as asthenia, anxiety, depression, sleep disturbances and other less frequent symptoms, such as temporomandibular disorders (TMD). **Data:** data were compiled by two experienced examiners following a specific form. **Sources:** An electronic search was carried out in the Cochrane Central Register of Controlled Trials (CENTRAL), PUBMED, and SCOPUS electronic databases (up to April 2016, unrestricted by date or language) **Study selection:** comparative clinical studies with patients with both clinical pictures involving the study of pathogenic processes. **Conclusions:** Fibromyalgia and temporomandibular disorders with muscle pain both have profiles that affect the muscular system and therefore share many epidemiological, clinical and physiopathological symptoms. Because of this, we are led to think that there is, if not a common etiology, at least a common pathogenesis. This article revises the physiopathological processes of both clinical pictures in an attempt to determine their similarities and likenesses. This would undoubtedly help in providing a better therapeutic approach.

Key Words: Temporomandibular Disorders. Fibromyalgia. Orofacial Pain. Pathogenesis

Introduction

Temporomandibular disorders (TMD), also known as temporomandibular joint dysfunction (TMJD), refer to a whole range of different clinical pathologies affecting the masticatory muscles and the temporomandibular joint. These pathological processes are mainly characterized by pain in the muscles or joints, dysfunction (limited or altered functions) and joint noises, accompanied by additional symptoms such as tension headaches, otalgia, dizziness, tinnitus and others. They are included in the "International Classification of Headache Disorders" under "headache or facial pain attributed to temporomandibular disorders (TMD)"[1]. Most classifications of TMD categorize them according to the etiology, into those that are congenital, due to tumor, inflammation, trauma or have a functional origin. The functional type has probably been the most controversial one concerning the etiology, and a multifactorial origin has been proposed.

Fibromyalgia (FM) is a syndrome of unknown etiology involving generalized chronic pain accompanied, in a high percentage of cases, by other symptoms, such as asthenia, anxiety, depression, sleep alterations and other less frequent symptoms, such as TMD.[2-4] Diagnosis is based on classificatory criteria laid down by the American College of Rheumatology revised in 2010 (the widespread pain index (WPI), a count of number of painful body regions, the symptom severity (SS) scale, a measure of cognitive symptoms, sleep, fatigue, and additional somatic symptoms) and marked by the absence of biochemical alterations in routine diagnostic tests.[5,6] Although, lately, CoQ10 deficiency has been associated to FM.[7,8]

Prevalence of TMD and FM

In industrialized countries, FM affects between 0.5 and 4% of the population and is 11 times more common in women than in men.[9-12] Some recent studies have described a prevalence of

3.4%, with 0.5% among men.[13] The results for TMD are very disparate because of the lack of homogeneity in diagnostic criteria in existing epidemiological studies. Taking some of the more recent ones as a reference, most agree that the prevalence is greater among women.[14-17] There are also epidemiological studies that associate TMD (with masticatory myofascial pain) and FM, which mention TMD rates that vary between 71% and 94% in patients with FM.[18-21] This percentage decreases considerably (to around 19%) when TMD pain is of arthrogenic origin.[21-24]

The prevalence of FM in patients with TMD, on the other hand, varies between 10 and 18.4%.[25-28] In these patients, the threshold of pain is lower and they present greater functional disability.[25,29,30] Although authors such as Schneider *et al.*[31] draw a distinction between the tender points that are characteristic of FM and the typical trigger points and taut bands of muscle of TMD,[31-33] other authors refer to the presence of trigger points in both clinical profiles, although they are fewer and localized differently in TMD patients.[33-35]

Temporomandibular disorders: Pathogeny

The etiology of TMD is considered to be multifactorial, although most authors have found a similar pathogenic process. Dawson *et al.*[36] states that TMD patients have higher blood levels of serotonin (5-HT) after exercising and a lower blood flow in the masseter muscle. These claims are supported by various studies, such as Guo *et al.*[37], who found that morphine and duloxetine, a selective serotonin reuptake inhibitor, attenuated the pain caused by ligation of the tendon of the masseter muscle in rats, and Okamoto *et al.*[38-41] whose well known studies in rats indicated that serotonin 5-HT2A and central 5-HT3 receptors in the spinal trigeminal nucleus, the trigeminal caudal subnucleus, and peripheral serotonin 5-HT2A and 5-HT1A receptors contributed to the process of nociceptive inflammation of masseter muscle.

In an experimental study, Oliveira *et al.*[42] found increased levels of serotonin (5-HT) in the synovial fluid of rats with inflammation of the TMJ (temporomandibular joint), which induced nociception by activating beta1- and beta2-adrenoreceptors located in the TMJ and releasing sympathetic amines and prostaglandins. Alstergren *et al*.[43,44] and *Kopp et al.*[45] also found high levels of serotonin 5-HT and interleukin-1beta in the synovial fluid of patients with TMJ arthritis and, in a similar study, Rodríguez *et al.*[46] showed that the release of norepinephrine contributes to the development of hyperalgesia by activating beta2-adrenoceptors. In another study, carried out in rats, Ting *et al.*[47] showed that histamine was able to induce TMJ pain by means of an indirect mechanism that involved the release of endogenous 5-HT and the activation of receptors on sensory afferents, so depolarizing the nociceptors by activating the serotonergic receptors. Fredriksson's e*t al.*[48] findings showed that local and systemic serotonergic mechanisms contributed to changing the pressure threshold in TMJ arthritis, while Voog *et al.*[49,50] suggested that serotonin 5-HT inhibitors reduced the intensity of movement pain in TMJ arthritis and that the intra-articular administration of the serotonin antagonist, granisetron, had an immediate but short-term soothing effect on the pain of temporomandibular joint inflammation. Nishimura *et al.*[51] referred to high levels of bradykinin and leukotriene B as causing vasodilation through the release of prostaglandins.

Lastly, serotonin-related studies have also pointed to a possible genetic factor in TMD. Meloto *et al.* [52] found an association between TMD and genetic polymorphisms in the estrogen alpha receptor, beta-2 adrenergic receptor, serotonergic receptor, serotonin transporter and catechol-O-methyltransferase genes, and Mutlu *et al*.[53] noted the possible involvement of the T102C polymorphism of the 5-HT2A serotonergic receptor in TMD. Herken *et al*.[54] found that the ST 2.10 allele of the serotonin transporter gene was more frequent in patients with TMD

pain. Ojima *et al.*[55] referred to the significant increase of longer L and XL alleles of the serotonin transporter gene in patients with TMD.

Fibromyalgia

Fibromyalgia (FM) is regarded as a nociceptive hypersensitivity of the central nervous system, in which stimuli that under normal circumstances would be harmless are interpreted in such a way as to produce an overwhelming and prolonged sensation of pain.[54-56] In this central hypersensitivity, various neurotransmitters with antinociceptive action, such as serotonin and noradrenaline[57-59] are involved in the nociceptive pathways in the spinal cord, as well as neurotransmitters of the proprioceptive network, such as substance P, GABA or glutamate[59-61] along with cannabinoid and opioid receptors and neurologic growth factors.[62] According to Napadow[65] however, nociceptive signal distortion in fibromyalgia does not only occur in the spinal cord; through affective and cognitive processes, other sensitive brain areas intervene in the subjective process of experiencing pain. Apart from augmented neuronal mechanisms, glial cell activation also appears to play an important role in the pathogenesis of fibromyalgia because they help to modulate pain transmission in the espinal cord and brain. Activated by various painful stimuli, they release proinflammatory cytokines, nitric oxide, prostaglandins, and reactive oxygen species that stimulate and prolong CNS (Central Nervous System) hyperexcitability.[66, 67]

The existence of mitochondrial alterations has also been clearly demonstrated in FM. In 1984, Kalyan-Raman *et al.*[68] described the presence of subsarcolemmal accumulations of mitochondria in muscle biopsies of patients with FM, and the same research team later described the alterations in mitochondrial structure as “abnormal”. More recently, in muscle biopsies of FM patients, Sprott *et al.*[69] observed that the mitochondria were fewer but larger. In 1993, Drewes *et al.*[70] observed deficient levels of oxidative phosphorylation in FM when cytochrome C-oxidase-negative fibers were identified showing a deficiency of the COX enzyme or of complex IV. These data along with subsarcolemmal aggregations and ultrastructural alterations in the mitochondria are characteristically found in mitochondrial diseases such as MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes) and MERRF (myoclonic epilepsy associated with ragged red fibers) and are used as diagnostic markers for them. Mitochondrial dysfuntion was also associated with increased expression of autophagia genes and the elimination of dysfunctional mitochondria with mitophagy. [8]

Jackson *et al* [71] demonstrated that oxidative stress can cause muscle damage and therefore be involved in many diseases like FM that affect the muscles.[69,70] In the past few years, several studies have demonstrated the presence of ROS markers in FM, which would confirm their involvement in the pathophysiology of the disease.[71-75,7,70] These researches confirmed, on the one hand, that patients with FM have a reduced total antioxidant capacity, due to the substantially diminished activity of superoxide dismutase (SOD), catalase and levels of glutathione[76-79,7]and, on the other, higher levels of ROS and hydrogen peroxide.[7] Lipid peroxidation (LPO) and carbonylated proteins are two markers of oxidative damage displayed in FM and high plasma levels of malondialdehide (MDA) have been observed as the final product of lipid peroxidation.[75,80,7,8]

Reduced platelet ATP levels have also been described in patients with FM[81] leading to the effects described previously in the muscle biopsies of such patients.[81,65] According to Bazzichi *et al.*[81] lower ATP levels in platelets could be involved in altered cellular homeostasis and so have an impact on the alteration of serotonin receptors, which are known to intervene in the nociceptive pathways. It is noteworthy that ATP synthesis has been proposed as a marker of

mitochondrial metabolism in the fibroblasts of patients with mitochondrial diseases.[68] In this respect, Cordero *et al*.[7] described low CoQ10 levels in the blood mononuclear cells of patients with FM as well as an increase in ROS levels, which later returned to normal after an *in vitro* CoQ10 supplement. Lower levels of CoQ10 led to a decline in the activities of mitochondrial complexes IIb, III and IV and reduced the expression of mitochondrial proteins involved in Oxphos, reducing mitochondrial membrane potential, increasing ROS production, activating the mitochondrial permeability transition pore, causing the degradation of dysfunctional mitochondria through a process of autophagy known as mitophagy, and restricting cell growth.[7, 8]

But what is the relationship between oxidative stress and the symptoms of FM? Previous studies have demonstrated that oxidative stress can cause peripheral and central sensitization of the nervous system and altered nociception leading to hyperalgesia, mediated by oxidative mechanisms in the local spinal cord.[82,83] Furthermore, tests have shown that oxidative stress increases in patients with chronic fatigue syndrome, with an interesting correlation with muscle symptoms.[84,85] This is because superoxide plays an important role in the development of pain, not just via direct peripheral sensitization, but also through the activation of cytokines (TNF-a, IL-1b and IL-6), peroxynitrite formation and PARP activation.[83] On the other hand, it has been observed a decrease in the antioxidants CoQ10 and catalase, as well as an increased level of LPO in blood mononuclear cells (BMCs) from FM patients compared to normal control.[86] In this work, oral CoQ10 supplementation restored biochemical parameters and induced a significant improvement in clinical and headache symptoms.

It should be remembered that, in comparison to other tissues, cells from the nervous system are very vulnerable to the toxic effects of free radicals because of the high levels of oxidative polyunsaturated fatty acids from the membrane.[82] Furthermore, a possible link has been observed between lipid peroxidation and depression, with a significant correlation between erythrocyte MDA levels and scores obtained on the Hamilton Depression Rating Scale[86], which are consistent with those obtained in FM.[75] Lastly, there is an important reduction in the function of serotonin reuptake inhibitors induced by LPO in patients who are more severely depressed,[87] as demonstrated in the important role of this oxidative process in depression, one of the main symptoms of FM.

Comparative physiopathology of the two clinical pictures

Very few studies in the revised literature have compared pathophysiological processes in patients with fibromyalgia and temporomandibular disorders (Table1). Studies by Ernberg *et al*.[89-92] and Hedenberg *et al*.[93,9] set out to determine the role of mediators like serotonin, prostaglandin E2 and leukotriene B4 in the pathophysiology of pain and inflammation of the masseter muscle in patients with TMD (local myalgia) and FM. They first determined intramuscular levels of the substances in the two clinical profiles, their clinical relationship and the effects on, after intramuscular glucocorticoid injection (0.3mm methylprednisolone).

The authors demonstrated that these mediators were present in the masseter muscle in both pathologies[90,91] and were associated with pain and allodynia[90], although the role that they each played in the two scenarios after the glucocorticoid injection[89,92] appeared to differ. In FM, a glucocorticoid injection led to lower serotonin levels, which did not occur in patients with local myalgia. The lower serotonin levels were also involved in the modulation of local muscle microcirculation since the intramuscular temperature decreased, which the authors interpreted as the result of vasoconstriction.[88] Likewise they indicated that, in patients with FM, there was a possible inflammatory process that was modulated by prostaglandin E2 and,

although the glucocorticoid injection did not significantly reduce the inflammation (which the authors claim may have been due to the increased levels of PG2 from the trauma caused by the needle itself), the authors associated a reduction in PG2 with reduced pain in the muscle.[91]

The fact that levels of leukotriene B4 increased in both clinical profiles after injecting the anti-inflammatory drug is both curious and difficult to explain; in the case of local myalgia, the increase was even associated with reduced pain and sensitivity on palpation. Ernberg *et al*.[90-92] also studied serum serotonin levels and concluded that, although they did not vary significantly between the two groups, there was a positive correlation in patients with TMD between high plasma serotonin levels and allodynia of the orofacial muscles. Therefore, while the clinical profile of FM seems to be muscular inflammation at the level of the masseter muscle with the possible mediation of serotonin and prostaglandin E2 (apart from other possible mediators), it is not so clear whether this process occurs in patients with local myalgia, although both substances were present. Therefore we deduce that the pathophysiological mechanism must be different, related more to systemic plasma serotonin levels than merely changes at a local level. The contribution of Light et al.[95] was dysregulation of beta-adrenergic activity in the set of symptoms associated with the two clinical pictures, which—as was the case with the serotonergic mechanisms and despite the fact that they shared the same pathophysiological mechanism—manifested differently in each clinical picture, with a slower heart rate, higher blood pressure and greater total vascular resistance being more striking in FM and a greater overall cardiac output in TMD.

Finally, although Gui *et al*.[96] found dysfunction of the masticatory muscles, with a positive correlation between surface EMG activity and pain during mandibular rest in both clinical pictures, there was also a difference, since higher median frequency values were associated with facial pain in patients with FM, which did not occur with patients suffering TMD only. Woda *et al*. (2013)[97] clearly showed that FM is characterized by a reduced ability to adapt to acute stress compared to TMD, which is consistent with the general hypothesis that, although they share inflammatory alterations and hyperalgesia, the mechanisms for reaching this state are different in each case (Table 1).

Concluding remarks

It would appear from the analysis of the two clinical pictures, separately and comparatively, that both FM and functional TMD share an neuroinflammatory etiology, although with some very interesting differential features, with clear alterations in the serotonergic mechanisms underlying nociceptive perception. Given the obvious mitochondrial dysfunction in FM, which causes increased oxidative stress y consecuentemente una sensibilización central y periférica del Sistema Nerviosos, pero además el aumento del estrés oxidative puede disminuir localmente el umbral del dolor en los tejidos musculares, it would be advisable to study whether there is also an alteration in oxidative balance.

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Table

Table 1.Studies associating FM and TMD					
Study	Main objectives	Sample size			
		FM	TMD	Control	Targer/markers symptoms
Ernberg M. et al. 1997.	Treatment effect of intramuscular GC injection differs in patients with FM and localized myalgia of the masseter muscle	25	25	-	Sensitivity withGC tretament
Ernberg M. et al. 1998.	The level of serotonin (5-HT) in the masseter muscle of administering IM glucocorticoid (GC) in patients with FM or localized myalgia (LM),	12	10	-	Serotonin with GC treatment
Ernberg M. et al. 1999 (108)	Whether serotonin is present in the human masseter muscle and, whether it is involved in the modulation of local muscle pain or allodynia.	18	17	-	Serotonin
Ernberg M. et al. 1999 (109)	Serum level of serotonin (S-5-HT) in patients with (TMD) of muscular origin, with healthy individuals and patients with FM. to investigate the association with pain parameters.	20	20	20	Serotonin
Hedenberg-Magnusson B. et al., 2001	Prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) in the masseter muscle and plasma, and their relation with myalgia.	19	19	11	PGE2and LTB4
Hedenberg-Magnusson B. et al., 2002	Masseter muscle (M) and plasma (P) levels of prostaglandin E2 (PGE2) or leukotriene B4 (LTB4) are influenced by local glucocorticoid administration and changes in local pain or hyperalgesia.	18	15	-	PGE2 with GC treatment LTB4 with GC treatment
Light KC et al. 2009	Cardiovascular, epinephrine (EPI), norepinephrine (NE), cortisol and clinical pain responses in patients with FM,TMD and controls.	10	10	16	EPI tenderness and NE with Bd Bp and Vr EPI and NE with Propanolol treatment
Gui MS. et al. 2013	Association between neuromuscular control and chronic facial pain in patients with FM and TMD.	27	28		EMG and pain
Woda A, et al. 2013	Differences in the mode of deregulation of a physiological response to a stressful stimulus by placing patients with FM, MF pain and controls under acute mental stress.	31	30	32	EMG activity and Stress and pain

Table 1.Studies associating FM and TMD.Results		
Study	**Fibromyalgia**	**Temporomandibular joint disorders**
Ernberg M. et al. 1997.	GC injection reduced sensitivity to muscle palpation.	GC injection reduced pain intensity and sensitivity to muscle palpation.
Ernberg M. et al. 1998.	GC injection reduced initial levels of serotonin (5-HT) in the muscle, and serotonin levels correlated negatively with intramuscular temperature.	GC injection reduced initial levels of serotonin but not significantly, negative correlation between serotonin levels and the threshold of pain to pressure
Ernberg M. et al. 1999 (108)	Levels of serotonin in the masseter muscle were higher than plasma levels	Levels of serotonin in the masseter muscle were lower than plasma levels
Ernberg M. et al. 1999 (109)	Levels of s S-5-HT similar between groups	Allodynia is related to S-5-HT and negative correlation with tenderness
Hedenberg-Magnusson B. et al., 2001	PGE2 and LTB4 were present in the masseter muscle correlated positively with pain ((PGE2)	PGE2 and LTB4 were present in the masseter muscle
Hedenberg-Magnusson B. et al., 2002	GC injection increased levels of LB4 did not alter levels of PGE2 but decreases pain and increase maximun mouth opening	GC injection increased levels of LB4 did not alter levels of PGE2 but decreases pain sensitivity
Light KC et al. 2009	Bd reduces the number of tender points. Plasma NE levels were lower than control . Heart rates and blood pressure increased with postural tasks and greater total vascular resistance compared to control.	Bd reduces the number of tender points. Plasma NE levels were lower than FM and control . Greater overall cardiac output and less total vascular resistance
	Differences in heart rate, EPI and NE levels disappeared after an iV injection of propranolol, and persisted those relating to blood pressure and total vascular resistance .	
Gui MS. et al. 2013	Increased surface EMG activity of the masticatory muscles correlated with increased facial pain at rest and premature interruption of masticatory muscle contraction	
	Positive correlation higher median frequency values and facial pain.	No positive correlation
Woda A, et al. 2013	Greater EMG reflex activity and higher pain response to stress	EMG reflex activity the same as for the control and Pain response to stress was greater than controls.

FM: Fybromyalgia;GC: Glucocorticoid; PGE2: Prostaglandin E2;EMG: electromyography;Bd: Beta-blockers;EPI: epinephrine;
NE: norepinephrine; LTB4: Leukotriene B4; S-5-HT: Serotonin;VR: Blood pressure and vascuiar resistance
PS: we found no studies that relate the pathogenesis of both diseases from 2014 to 2016

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