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Myofascial Temporomandibular Disorder

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Abstract: Temporomandibular disorders (TMD) have been discussed for more than 70 years without reaching consensus on causes, etiological factors, pathophysiology, or rationale management. Indeed, TMD pain remains an enigma and a diagnostic and management challenge for many clinicians. Perhaps the many and often conflicting views on TMD pain by different health care providers are routed in professional traditions, personal beliefs, experience, and clinical training. This review aims to provide an updated and critical discussion on what is known and supported by scientific evidence about myofascial TMD pain and which gaps there still may be in our understanding of this condition. It has not been the intention to make a systematic review on all aspects of TMD but rather to point out some of the more recent (and important) pieces of information that may help us to better appreciate TMD pain as a complex and multifaceted pain disorder manifested in the craniofacial system.

Keywords: Temporomandibular pain, sensitization, treatment, patient-centered management.

INTRODUCTION

Temporomandibular disorder (TMD) is a term including different conditions involving the temporomandibular joint (TMJ), the masticatory muscles and their associated tissues (e.g. ligaments, connective tissues) that represents a clinical problem such as pain, limited jaw movements and TMJ noises. Several studies on different aspects have been conducted to improve understanding, diagnosis and management of this patient population. Since TMD pain has been suggested to be included into the concept of Central Sensitivity Syndromes [1], the current article summarizes current data on epidemiology, clinical features, differential diagnosis, pathophysiology, and management related to patients suffering from myofascial TMD-related pain.

EPIDEMIOLOGY

The lifetime prevalence of TMD is unclear, but some studies have shown prevalence rates ranging between 3% and 15% in the Western population, and incidence rates between 2% and 4% [2]. It seems to be a peak around 20-45 years for women although elderly people may also suffer from TMD pain, particularly associated with degenerative changes in the joint [3]. Isong *et al.* determined that the overall prevalence of TMD pain was 4.6%, with 6.3% for women and 2.8% for men (ratio 2:1) [4]. Nevertheless, these studies did not differentiate between myofascial and arthralgia TMD.

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It seems that myofascial TMD pain (single or multiple diagnoses) is the most frequent diagnosis (42%) in patients with orofacial pain, followed by disc displacement with reduction (32.1%) or arthralgia (30%) [5]. Janal *et al.* reported that the prevalence of myofascial TMD was 10.5% (95%CI 8.5%-13.0%) in a New York metropolitan area [6]. In this study, prevalence of myofascial TMD pain was significantly higher in younger, black and non-Hispanic women [6]. Balke *et al.* found reported that the frequency of myofascial TMD, disc displacement, and degenerative disorders was greater in the rural area than in those leaving in urban areas [7].

A meta-analysis including 21 epidemiological studies and a total of 3,463 subjects with orofacial pain concluded that the overall prevalence for myofascial TMD pain (group I muscle disorder-RDC/TMD criteria) was 45.3%, whereas the prevalence of disc displacement (group II-RDC/TMD criteria) was 41.1% [8]. This review also observed that studies on general populations including 2,491 subjects reported an overall prevalence of 9.7% of myofascial and 11.4% of disc displacement [8]. Nevertheless, the prevalence of myofascial TMD is higher in subjects with particular conditions such as those with later whiplash syndrome [9] or with gastroesophageal reflux disease [10].

Further, myofascial TMD is commonly comorbid with other entities, e.g., headaches. Gonçalves *et al.* found that individuals with myofascial TMD were significantly more likely to suffer from chronic daily headaches (relative risk (RR: 7.8; 95%CI 3.1-19.6), migraine (RR: 4.4; 1.7-11.7), and tension-type headache (RR: 4.4; 1.5-12.6) in comparison with individuals without TMD pain [11].

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Finally, the prognosis of myofascial TMD is controversial. Rammelsberg *et al.* found, in a 5-year longitudinal study, substantial variations in the time course of myofascial TMD with 31% being persistent, 33% being remittent and 36% recurring [12]. Overall, there is a need for longitudinal studies with well-described groups e.g. according to the Diagnostic Criteria for TMD pain, to better understand the prevalence, incidence, trajectories and prognosis [13].

CLINICAL FEATURES

TMD is not a single entity but rather a cluster of related conditions in the masticatory muscles, temporomandibular joint (TMJ) and associated surrounding structures. TMD pain is characterized by a classically triad of clinical features: muscle and/or joint pain; TMJ sounds (in the case or disc displacement or degenerative joint disorders); and restriction, limitation, deviation, or deflection of the mandible during opening and closing movements [14].

One of the common clinical features of TMD includes spontaneous face pain or pain on mandible motion in the orofacial region. Patient-based drawings of their pain symptoms demonstrate a concentration around the masseter muscle and spreading to the temporalis muscle. This is typically cardinal symptom in those patients with a diagnosis of myofascial TMD pain; although not exclusive of this condition. Alonso-Blanco *et al.*, using a new technique such as the calculation of the center of gravity of patient-based pain drawings, were able to determine the anatomical location of usual symptoms in the orofacial region in women with myofascial TMD and found that symptoms of women with myofascial TMD pain were mainly located in the lateral part of the masseter muscle and the eyes (Fig. **1**) [15].

Another typical clinical sign of myofascial TMD is the tenderness or pain on palpation of muscle structures, particularly the masticatory musculature. In fact, masticatory muscles are easily accessible to manual palpation, and some authors have standardized the areas that should be explored, and even the pressure and time to be applied; however, no consensus is reached on this topic although the recommendation from the DC/TMD specifies 1 kg for 2 seconds to be applied to the masseter and temporalis muscle, and 0.5 kg to the TMJ [13]. It should also be noted that simple mechanical devices can be used to eliminate most of the variability associated with manual palpation of the jaw muscles [16, 17]. This sign (increased pain on palpation) is probably related to the presence of sensitization mechanisms (they will be discussed later in this manuscript) with also include presence of myofascial trigger points (TrPs) [18]. The main difference between tenderness and TrPs is the presence of referred pain elicited by manual palpation (this topic will be also discussed later) [19].

Other clinical features associated with myofascial TMD could include parafunctional habits, presence of tooth clenching, limited jaw opening, although these features can be also associated to TMJ arthralgia [14]. The mandibular movements usually assessed in clinical practice include maximum opening (passive/active with/without pain), maximum excursions to both sides, and maximum protrusion. However, restricted mandibular movements do not provide relevant information for any specific diagnosis since multiple reasons can be related to this impairment (e.g., TMJ ankyloses, muscle contracture, Eagle syndrome). Other clinical signs such as TMJ clicking are usually more associated to TMD of joint origin, e.g., displaced discs.

Benoliel *et al.* found that the presence of pain-related awakening was higher in patients with myofascial TMD than in individuals with trigeminal neuralgia and this was associated with higher muscle tenderness (OR 1.13, 95%CI 1.01-1.3) and the presence of unilateral orofacial pain (OR 3.9, 95% CI 1.2-12.3) [20]. Nevertheless, some authors suggest that clinical features of myofascial TMD seem to be more related to psychological changes, e.g., stress, depression, anxiety, neuroticism, catastrophist attitudes, rather than to physical parafunctional activities [21]. Table **1** summarizes potential signs and symptoms of patients with myofascial TMD.

DIAGNOSIS

TMD diagnosis is mainly based on a combination of defined signs and symptoms. The most accepted and worldwide used diagnostic criteria are the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) proposed in 1992 [22] - now being replaced by the validated Diagnostic Criteria for TMD (RC TMD) [13]. Furthermore the classification of the American Academy of Orofacial Pain (AAOP), first published in 1993 [23], is often used in clinical settings. Within the RDC/TMD, axis I and axis II are mainly included, with three major diagnostic categories contemplated in the axis I: myofascial pain, disc alterations and arthralgia-arthritis-arthrosis [22]. The DC/TMD uses the same double axes approach with three major groups related to muscle pain, TMJ disorders, and headache attributed to TMD. John *et al.*, in an international multi-center study, found moderate

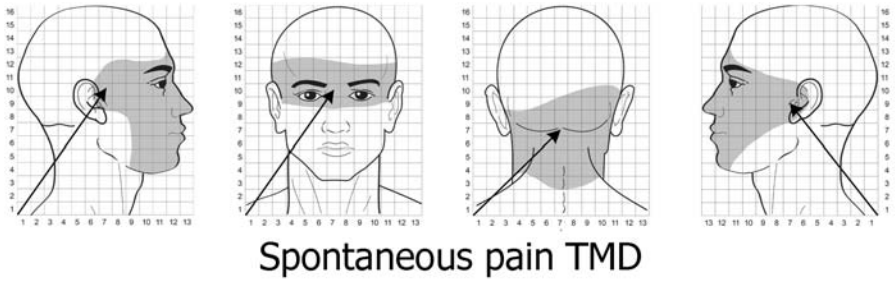

Fig. (1). Pain pattern of the symptoms in a patient with myofascial TMD pain.

Table 1. Clinical Features of Myofascial Temporomandibular Pain (TMD) and Potential Questions suggesting the Presence of Sensitization.

Symptoms of myofascial TMD	Clinical signs of myofascial TMD
Spontaneous pain in the temporomandibular joint	Restriction of mouth movements
Spontaneous pain mainly focused in the masseter and temporalis areas	Deviation or deflection during mouth movements
Joint clicking (more frequent in joint diseases)	Tenderness to palpation of the joint or masticatory muscle
Other associated symptoms such as parafunctional habits or tooth clenching (not always)	
Potential Questions suggesting the Presence of Sensitization	
Do you usually suffer from pain in a different region than the face?	
How often does the pain change in quality, form, duration or sensation?	
Do you suffer from pain in different parts of the body at the same time?	
Do you have a restorative sleep? Does the pain reduce the quality of sleep?	
Do you perceive fatigue, not in the mouth, in the body?	
Do you have other non-musculoskeletal pain symptoms, e.g., stomach ache?	

reliability (ICC: intra-class correlation coefficients) for diagnoses of myofascial TMD pain with (ICC 0.51) and without (ICC: 0.60) limited mouth opening [24]. In a more recent study, Look *et al.* reported that reliability of RDC/ TMD diagnoses was excellent (kappa values>0.75) when myofascial TMD diagnoses were grouped [25]. Good reliability was also observed when myofascial TMD diagnoses were not grouped (Ia - myofascial pain without limited mouth opening - kappa: 0.62; Ib - myofascial pain with limited mouth opening - kappa: 0.58). Nevertheless, these diagnostic criteria are not as clear as they seem to be applied in epidemiological studies since more than one RDC/TMD diagnosis is usually presented in 35.2% of the patients [5]. Future epidemiological studies should apply the unique DC/TMD system since this is the diagnostic system with documented key information about validity (sensitivity and specificity). Although the RDC/TMD has been one of the most successful approaches to pain-related TMD diagnoses, several modifications were needed [26]. Therefore, the "International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group" has recently proposed and published a modification (DC/TMD) in the axis I for improving the diagnosis reliability and validity [13]. This modified axis I protocol includes diagnostic criteria showing sensitivity and specificity values ranging from 0.7 to 0.95 [13]. Further, the recent expanded taxonomy for DC/TMD has added further diagnoses for myofascial TMD pain group; 1, local myalgia: patients reporting local muscle pain limited to the palpation site; 2, myofascial pain: patients reporting pain at the palpation site that would spread beyond the palpated area but remain inside the boundary of the examined muscle; 3, myofascial pain with referral pain pattern: patients reporting pain at the palpation site and pain referral beyond the boundary area of the examined muscle [13]. Nevertheless, it seems clear that future clinical and basic research is still needed to further determine and clarify the mechanisms underlying the different diagnostic criteria for myofascial TMD pain [27].

DIFFERENTIAL DIAGNOSIS

Although RDC/TMD criteria and the new DC/TMD seem to be appropriate for myofascial TMD diagnosis, there are several other pain syndromes resembling similar clinical sign and symptoms. For instance, symptoms from myofascial TMD are very similar to those experiencing by individuals with tension type headache (TTH). For instance, the third edition of International Classification of Headache Disorders (ICHD-III) describes a headache attributed to TMD [28]. This is also recognized in the DC/TMD with similar, but validated criteria for Headache attributed to TMD [13]. Therefore, patients with similar clinical sign and symptoms can receive a different diagnosis depending on the doctor that they seek for. Svensson suggested that carefully assessment of the subject-based pain drawings could help to first distinguish if the predominant condition is the head or the facial pain [29]. This assumption was based on the result of an experimental pain model showing that myofascial TMD pain is more similar to the pain patterns produced by injections into the masseter muscle and that TTH symptoms are is more similar to the pain patterns evoked by painful stimulation of the neck musculature, i.e., the splenius or upper trapezius muscles [30]. Nevertheless, other muscles such as the temporalis muscle can be similarly involved in both conditions.

Another chronic pain condition that is usually comorbid with myofascial TMD but it can also exhibit similar sign and symptoms is fibromyalgia syndrome (FMS). For instance, Pimentel *et al.* found that facial pain was reported by 85% of the FMS group and 77.5% were diagnosed with myofascial TMD [31]. Similarly, Fraga *et al.* reported that the most common signs and symptoms reported by individuals with FMS were pain in the masticatory muscles (masseter, 80%; posterior digastrics, 76.7%), pain in the temporomandibular joint (83.3%), headaches (97%) and facial pain (81.7%) [32]. Nevertheless, some of these clinical features have been found to be different between individuals with FMS and myofascial TMD since muscle pain during jaw movements, daytime bruxism/clenching, and limited mouth opening were

significantly higher in individuals with myofascial TMD than in those with FMS [32]. This cluster of signs and symptoms could help to differentiate a primary diagnosis of myofascial TMD against a primary diagnosis of FMS; although both entities are sometimes considered within the same concept of central sensitivity syndromes (see discussion on pathophysiology).

Additionally, Alonso-Blanco *et al.* observed that referred pain elicited by trigger points (TrPs) in women with FMS was mostly located in the neck, whereas TrP referred pain in women with myofascial TMD was mostly located in the face area [15]. However, this simple differentiation seems to be insufficient for a proper differential diagnosis.

PATHOPHYSIOLOGY

Although the etiology and pathology of TMD is still under debate, there is evidence of multiple factors acting at the same time. The current section will review all possible factors related to pathophysiology of myofascial TMD pain focusing on the presence of facilitated nociceptive processes.

SENSITIZATION MECHANISMS

There is clear scientific evidence suggesting the presence of peripheral and central sensitization mechanisms in patients with myofascial TMD. *Peripheral sensitization* is related to an increased responsiveness and reduced threshold of peripheral nociceptors to stimulation of their receptive fields. It is characterized by an increased spontaneous activity, a decreased response threshold to noxious stimuli, increased responsiveness to the same noxious stimuli, and/or increased receptive field sizes. *Central sensitization* is defined as increased response to pain stimulation mediated by amplification of signaling to the central nervous system and can occur through two main mechanisms: an increased excitation (sensitization) or decreased pain inhibition (descending facilitation).

Muscle pain is mainly featured by the presence of peripheral sensitization of nociceptors which explain deep tissue hyperalgesia at the injured area [33]. Different substances can sensitize primary muscle nociceptive fibers. Particularly effective stimulants for muscle nociceptors are endogenous substances such as substance P, glutamate, bradykinin or serotonin. In fact, some experimental pain studies have reproduced similar pain patterns than those experienced by individuals with myofascial TMD by injecting hypertonic saline [34], glutamate [35] or capsaicin [36] in healthy people. The role of these substances and their receptors are discussed later.

In the last decade, several studies have investigated the role of the nociceptive system in patients with myofascial TMD by assessing trigeminal and extra-trigeminal pain sensitivity in patients with TMD pain. In such scenario, trigeminal hypersensitivity may be considered as a manifestation of sensitization in the trigeminal area (peripheral sensitization) whereas extra-trigeminal hypersensitivity would be a manifestation of sensitization in distant pain-free areas (central sensitization). There is clear evidence supporting that both sensitization processes are implicated in the pathophysiology of myofascial TMD [37].

Several studies support the presence of trigeminal pain hypersensitivity to different stimuli such as pressure or thermal in patients with myofascial TMD. In fact, several studies have reported the presence of pressure pain hyperalgesia, expressed as decreased pressure pain thresholds (PPT), in the masseter and temporalis muscles in patients with myofascial TMD [38-41]. It seems that the masseter muscle is the most sensitive to pressure pain of the masticatory musculature [42]. Further, pressure hyperalgesia is not influenced by menstrual phases in women with myofascial TMD [40]. This hyper-excitability of the trigeminal region is also expressed as a pronounced temporal summation of pain and greater after-sensation following repetitive noxious mechanical stimulation in the masseter region [43]. Maixner *et al.* found thermal C-fiber-mediated temporal summation expressed as lower heat pain thresholds and greater magnitude of sustained noxious heat pulses over the masseter region in patients with myofascial TMD pain [44]. Pressure or thermal pain hypersensitivity in the masticatory muscles reflects sensitization of primary nociceptive afferents of muscle tissues in this patient population.

Other studies have revealed that individuals with myofascial TMD also exhibit extra-trigeminal pain hypersensitivity to different stimuli. A number of studies consistently found that individuals with myofascial TMD exhibit widespread pressure pain hypersensitivity as expressed by lower PPT over different deep tissues, e.g., muscle, joint and nerve, in both trigeminal and extra-trigeminal pain-free areas [37, 45-47]. However, the results on thermal pain sensitivity are conflicting since some studies reported thermal pain hyperalgesia in both trigeminal and extra-trigeminal regions in individuals with myofascial TMD [48-50], whereas others did not [45, 51]. These findings are supported by a large case-control study including 185 patients with TMD and 1,633 healthy controls which concluded that the largest differences between patients with TMD and healthy controls are observed in pressure pain sensitivity at multiple body sites, whereas heat pain sensitivity exhibited lesser effect sizes [52].

These results would support the hypothesis that myofascial TMD pain is characterized by sensitization processes not only restricted to the trigeminal second order neurons, but also to extra-trigeminal nociceptive neurons as previously suggested. It is important to note that this central sensitization process observed in patients with myofascial TMD is similar to the sensitization processes reported in local [53-56] and widespread [57-59] pain conditions. Nevertheless, the magnitude of this sensitization seems to be higher within the trigeminal area of patients with myofascial TMD pain [45, 47]. In addition, the relevance of trigeminal sensitization is further confirmed by the fact that widespread pressure pain hypersensitivity is associated with the intensity and duration of the symptoms [47].

The clinical relevance of sensitization mechanisms in myofascial TMD is supported by the fact that two subgroups of patients have been identified: sensitive (> 11 tender points) and insensitive (< 11 tender points) patients with TMD [60]. This classification was based on the number of tender points used for the diagnosis of fibromyalgia syndrome (fibromyalgia tender point count). This study found

that the sensitive subgroup exhibited enhanced pain responses to pressure and thermal stimuli in both trigeminal and extra-trigeminal areas than the non-sensitive TMD group [60]. Clinical repercussions of this classification are discussed later.

WIDESPREAD SYMPTOMS

Additionally, clinical evidence consistent with the principle that myofascial TMD is associated with central sensitization is that patients often report persistent pain in multiple body areas [61]. This study found that only 19% cases exhibited pain limited to the trigeminal system and that 2 additional pain patterns were present: 1, patients with pain in the trigeminal dermatomes and pain in c2-C4 spinal dermatomes (neck pain, 16%); and, 2, individuals with pain involving additionally dermatomes (n = 65%) [61]. In fact, Pfau *et al.* observed that the sensitive myofascial TMD subgroup exhibited more expanded pain areas on superimposed pain drawings than the non-sensitive subgroup [60].

Myofascial TMD pain is usually diagnosed on fibromyalgia subjects, and vice versa, patients with fibromyalgia syndrome also fulfill diagnostic criteria for myofascial TMD [31, 32]. For instance, Leblebici *et al.* showed that myofascial TMD was reported in 80% of individuals with fibromyalgia syndrome, whereas 52% of patients with myofascial TMD fulfilled diagnostic criteria for fibromyalgia syndrome [62]. In fact, it seems that the presence of widespread pain is a risk factor for the onset development of TMD pain (OR 1.9, 95%CI 1.2-2.8,) in women but not in men (OR 1.0, 95%CI: 0.4-2.8) [63]. This assumption was supported by Velly *et al.* who observed an increased risk for the onset of clinically TMD pain when subjects were diagnosed with fibromyalgia (adjusted OR 2.74) or widespread pain (adjusted OR 2.53) [64]. However, this study also found that fibromyalgia, but not widespread pain, predicted not only the onset, but the persistence of clinically significant TMD pain to a more severe condition (adjusted OR 2.49) [64]. A specific mechanism to explain these estimated risks has not been yet identified, but these associations support the concept that widespread pain, fibromyalgia syndrome and myofascial TMD pain can be considered as Central Sensitivity Syndromes [1].

Therefore, the overwhelming conclusion from clinical and scientific evidence is that central nervous system hypersensitivity can result in apparently phenotypically different pain syndromes depending on the tissue affected. However, the overall similarity of the sensitivity changes may reflect a common contribution of central sensitization mechanisms, and this may account for the high co-morbid rate of the apparently different pain syndromes [65]. Table **1** shows some questions that can be used in localized chronic pain syndromes that could assist clinicians to suspect of sensitization mechanisms in patients with myofascial TMD.

FUNCTIONAL BRAIN IMAGING

In the last decades, central pain processing has been assessed with imaging techniques looking at cerebral blood flow changes following nociceptive stimuli in several chronic pain syndromes [66]; however, relatively few neuroimaging studies of TMD pain exist. Younger *et al.* found the presence of altered brain morphology in areas related to pain in individuals with TMD pain [67]. This study revealed that patients with myofascial TMD exhibited decreases in gray matter volume in several areas of trigemino-thalamo-cortical pathway including brainstem trigeminal sensory nuclei, thalamus, and the primary somatosensory cortex, and an increased gray matter volume in some limbic regions, e.g., posterior putamen, globus pallidus, and anterior insula, as compared with healthy controls [67]. This pattern of gray matter abnormality suggests the involvement of trigeminal and limbic system dysregulation, as well as potential somatotopic or structural reorganization within the putamen, thalamus, and somatosensory cortex in myofascial TMD [67]. Finally, this study also found that the intensity of pain was associated with increased gray matter within the rostral anterior cingulate cortex and posterior cingulate, supporting a role of the trigeminal nociceptive inputs in brain changes. Similarly, Gerstner *et al.* also reported decrease in gray matter volume in the left anterior cingulate gyrus, right posterior cingulate gyrus, the right anterior insular cortex, left inferior frontal gyrus, and the superior temporal gyrus in individuals with TMD pain, supporting the presence of changes in brain morphology in areas integrated into the central pain system [68]. A meta-analysis has recently concluded that patients with TMD showed consistent functional/structural changes in the thalamus and the primary somatosensory cortex, indicating the thalamo-cortical pathway as the major site of brain plasticity in this population [69].

Some authors discussed these data as atrophy, reinforcing the idea of damage or loss of brain gray matter [66]; however a decrease in the brain gray matter does not always mean neuronal destruction. Independent of the exact nature of the brain changes, it is well accepted that chronic pain patients exhibit a decrease in gray matter as a common feature, and while the exact loci differ between pain conditions, there seems to be overlap in some areas including cingulate cortex, thalamus, insula, basal ganglia, dorso-lateral prefrontal cortex and brainstem [66]. Nevertheless, whether these observed brain abnormalities are cause or consequence of chronic pain is not fully determined [70]. In fact, different hypotheses have been proposed. One hypothesis is that gray matter abnormalities represent neuroplastic chronification or learning of pain. Another one is that the observed brain changes represent pre-existing vulnerabilities to chronic pain. A third possibility is that brain abnormalities are simply adaptations of the central nervous system to aberrant peripheral nociceptive inputs [70]. The fact that most of imaging studies conducted in chronic pain condition revealed significant correlations between brain gray matter changes and the duration or intensity of the pain, suggest that these brain changes may be the consequence of pain [71]. This hypothesis was confirmed by the study of Rodriguez-Raecke *et al.* where the gray matter decreases were partly recovered when the pain (the peripheral nociceptive stimuli) was successfully identified and properly treated [72].

Future clinical studies should investigate the prognosis or changes observed in brain gray matter after proper management of individuals with myofascial TMD with multimodal approaches. Furthermore, functional brain imaging studies may identify potential overlapping neuronal networks in response to the processing of different sensory painful mo-

dalities, i.e., understanding multisensory integration in myofascial TMD pain patients may be important for understanding the pain.

PSYCHOLOGICAL FACTORS

There is clinical evidence supporting the relevance of psychological factors in patients with myofascial TMD. In fact, the OPPERA study clearly demonstrates that myofascial TMD is a complex disorder consistent with a biopsychosocial model of illness [73]. Several studies have observed an association between myofascial TMD and anxiety, depression, stress, mood and somatization [74-77]. It seems that the presence of anxiety and depression increases the likelihood of having higher muscle tenderness [78] and higher pressure pain hypersensitivity [79] in patients with orofacial pain. More recently, Kindler *et al.* found that anxiety predicted the new onset of TMD muscle pain [80]. The OPPERA study recently concluded that somatic symptoms, general psychological symptoms, negative mood, symptoms of posttraumatic stress and stress emerged as risk factor for incident TMD pain [81]. Further, the association between depression, perceived stress, and mood in patients with myofascial TMD is independent of the effects of the Val158Met haplotype of the catechol-O-methyltransferase (COMT) gene [82].

Manfredini *et al.* found that subjects with myofascial TMD exhibited higher prevalence of mood and panic-agoraphobic symptoms than patients with other TMD diagnosis. Patients with myofascial TMD exhibited higher stress, panic, separation anxiety, hypochondriac and agoraphobic symptoms than the remaining TMD groups [83]. Nevertheless, although it is clear that patients with myofascial TMD exhibit higher levels of anxiety, depression, stress, mood and somatization, none published study has been able to demonstrate causality of that relationships. Some hypotheses are proposed discussing possible predisposing, triggering or worsening role of psychological disorders in patients with TMD [84]. Future longitudinal studies investigating the prognosis role of psychological disorders in the onset of myofascial TMD and the effects of proper management of this disorder are needed.

Other authors discuss the role of catastrophization in patients with myofascial TMD. Catastrophizing is considered a negative cognitive-affective response to different pain stimuli involving rumination, helplessness, and magnification [85]. Catastrophizing has been linked to self-reported pain, activity interference, negative mood, greater clinical exam findings, and increased health care utilization in patients with TMD [86]. In fact, catastrophizing explained significant proportions of the variance in activity interference (14%), non-masticatory jaw activity limitations (18%), and depression (33%) [87]. Velly *et al.* found that depression and catastrophizing contribute to the progression of chronic pain and disability in patients with TMD pain [88]. Further, it seems that the rumination, but not helplessness and magnification, component of catastrophizing is related to clinical outcomes through alterations in sleep [89]. The neurophysiological substrate of pain catastrophizing has not been yet determined. Quartana *et al.* observed that catastrophizing was associated with a flattened morning salivary cortisol profile in the context of laboratory pain testing in both healthy people and patients with myofascial TMD suggesting that aberrant adrenocortical responses to pain may serve as the neurophysiologic pathway by which catastrophizing enhances vulnerability for development of chronic pain and maintains and/or exaggerates existing pain [90].

Another important psychological aspect is the ability of self-efficacy of the patients for managing their pain, that is, coping strategies [91]. Aaron *et al.* showed that patients with TMD use a variety of treatment, self-care, and coping strategies to contend with daily pain; however these strategies were not able to produce proper management and control of pain [92]. A study found that coping explained 13% of the variance in activity interference, without any association with depression [87]. In fact, appropriate management of coping strategies was modestly associated with patient improvement after conservative dental treatment [93].

Finally, the last psychological factor that should be mentioned is the hyper-vigilance. A hyper-vigilant individual is someone who is unusually alert to ''somatic distress signals" including, but not limited to, pain. Therefore, hypervigilance causes amplification of aversive sensations by increasing nociceptive perception. Hollins *et al.* showed that individuals with chronic myofascial pain, especially those with high levels of hyper-vigilance, exhibited robust perceptual amplification for some types of stimuli [94].

Current evidence supports a relevant role for psychological factors in individuals with myofascial TMD and therefore should be considered as important factors when developing treatment plans for patients with TMD. A potential neurophysiological mechanism explaining these complex relationships may be related to the fact that individuals with myofascial TMD exhibited increased gray matter volume than healthy people in the anterior insula [67]. The anterior insula is a limbic-associated structure involved in the integration of emotional and bodily states being critical in interoception or the emotional awareness of internal states [95], as well as the emotional aspects of the pain experience [96] and anticipation of sensation [97].

SLEEP DISORDERS

There is some evidence suggesting the possibility that sleep disturbance may directly contribute to central sensitization and pain amplification in patients with myofascial TMD. The literature has mainly focused on possible relationships between sleep bruxism and TMD; however, sleep bruxism is not associated with poor sleep quality [98] and the potential causal relationships between sleep bruxism and TMD is controversial [99].

Riley *et al.* observed that around 50% of patients with TMD pain report poor sleep quality associated with psychological distress and worse pain symptoms [100]. Similarly, Smith *et al.* showed that individuals with TMD diagnosed with primary insomnia, sleep apnea, or sleep bruxism exhibited increased anxiety symptoms, increased symptoms of depression, and increased pain severity [101]. Additionally, TMD patients with diagnosis of primary insomnia presented generalized pain hyperalgesia [101]. The fact that primary insomnia was associated with generalized pressure hyperal-

gesia suggests that primary insomnia may either share a common substrate underlying central hypersensitivity and/or play a causal role in the development of hyperalgesia in patients with TMD pain. In line with this hypothesis, it has been demonstrated that reduced sleep efficiency is associated with impaired pain-inhibitory function in patients with TMD [102]. In such way, disrupted sleep may also serve as risk factor for inadequate pain-inhibitory processing. The relevance of sleep disorders and their relevance for therapeutic approaches to prevent TMD pain had been also pointed out in the OPPERA study [103].

IMMUNOLOGIC FACTORS

Although less explored than other patho-physiological impairments, there is growing consensus that altered basal and stress-induced hypothalamic-pituitary-adrenocortical (HPA) activity may exist in myofascial TMD. It is known that the HPA axis is the major centrally regulated endocrine system responsible for rapid and strong responses to stress, and that stress activates this axis and sympathetic nervous system. Disruption in these systems potentiates the release of cortisol and other chemical mediators, increasing and promoting pain. In fact, a higher imbalance in the HPA axis may be related to worse adaptation responses to stress.

Some studies have reported that patients with myofascial TMD exhibit an increased cortisol response than healthy people to psychological stress [104] and greater daytime plasma-cortisol and adrenaline levels than matched controls [105, 106]. Nadendla *et al*. have recently observed that higher salivary cortisol levels were positively associated with higher levels of anxiety in a cohort patients with myofascial TMD pain [107]. On the contrary, others have not reported such differences in cortisol levels between patients with myofascial TMD pain and healthy people [108, 109]. Interestingly, proper management of pain with occlusal appliances did not modify cortisol, immunoglobulin A (IgA) and flow rate values in patients with myofascial TMD pain [110]. This study suggests that commonly pain management is not enough to restore HPA axis impairments in TMD pain.

Interaction between the peripheral nervous system (sensory and sympathetic nerves), the immune system, and local cells seems to be of great importance for the modulation of pain and inflammation orofacial muscles [111]. Further, estrogens are implicated in myofascial TMD pain and have an impact on the function of the immune system which adds to the complexity of understanding the significance of immunological factors in TMD pain [112].

NEUROTRANSMITTERS/NEUROPEPTIDES

There is evidence supporting a relevant role for different neuropeptides in TMD pain. Glutamate, the endogenous agonist for excitatory amino acid (EAA) receptors, seems to play an important role since it may modulate nociceptive processing inputs from deep craniofacial tissues and cause sensitization [113].

The concentration of glutamate in the masseter muscle of patients with myofascial TMD pain was significantly higher than the concentration in healthy controls [114], in agreement with some studies on patients with chronic trapezius myalgia [113]. Castrillon *et al.* found that characteristics of pain generated by intramuscular injection of glutamate in the masticatory musculature vary for different muscles and may be partially generated through activation of peripheral N-methyl-D-aspartate (NMDA) receptors [115]. Surprisingly, local administration of ketamine in the painful masseter muscles of individuals with myofascial TMD pain did not decrease the clinical pain levels more than a placebo administration suggesting either too low doses were used to adequately block the NMDA receptors or a significant contribution by other neurotransmitters or neuropeptides [116].

Experimental inflammatory conditions of the TMJ and pericranial muscles lead to changes in the central nervous system which can be reversed with central delivery of NMDA antagonists [117]. Wong *et al.* have recently reported that NGF-induced sensitization of masseter nociceptors is mediated, in part, by enhanced peripheral NMDA receptor expression [118]. Indeed NGF-related mechanisms may be involved in prolonged sensitization of muscle tissue [119-121].

There is good evidence that also serotonergic mechanisms may be at play in patients with myofascial TMD pain [113]. Serotonin (5-HT) is a small monoaminergic molecule with significant impact on pain processing both in the peripheral and central nervous system. In fact, it has been suggested that serotonin may be the best candidate as a potential biomarker for chronic myofascial pain. This suggestion is based on the findings of elevated serotonin levels in patients with myofascial TMD pain and correlations between muscle-5-HT level and clinical pain as well as pressure pain thresholds [113]. Other mediators such as bradykinin, prostaglandins, leukotrienes, cytokines, substance P (SP) and calcitonin gene-related peptide (CGRP) have also been implicated in myofascial TMD pain but their overall significance to clinical pain and sensitization has not yet been established in either microdialyses studies or intervention studies [113].

It has also been convincingly demonstrated that activation of vanilloid (TRPV1) receptors in muscles by injections of capsaicin lead to ongoing pain and sensitization effects [122-124]. Moreover, TRPV1 receptor up-regulation at the trigeminal ganglion level and bilateral allodynia has been demonstrated in response to experimental masseter myositis in rats [125]. It has been suggested that TRP channels expressed in muscle afferents can participate in development of pathologic muscle pain conditions [126] but clinical studies will be needed to further substantiate this claim.

Single-voxel proton magnetic resonance spectroscopy was used before and after pressure-pain testing to assess glutamate (Glu), glutamine (Gln), N-acetylaspartate (NAA), and choline (Cho) levels in the right and left posterior insulae of 11 subjects with myofascial TMD and 11 healthy controls. Among those with TMD, left-insular Gln levels were related to reported pain, left posterior insular NAA and Cho levels were significantly higher at baseline than in control individuals, and NAA levels were significantly correlated with pain-symptom duration, suggesting adaptive changes. The results suggest that significant central cellular and molecular changes can occur in individuals with TMD [127]. Clearly the identification of neurotransmitters and neuropeptides as potential biomarkers of myofascial TMD pain either in the

peripheral or central nervous system is an intriguing research area with potential implications for prognosis and management.

GENETICS

There is an increasing interest in understanding the importance of candidate risk genes and their contribution to pain conditions. TMD pain seems to be influenced by multiple genetic variants of relatively high minor allele frequency, particularly related to disturbances in catecholamine, serotonin, opioid, and cytokine pathways [128]. Several genes are currently involved in myofascial TMD pain; nonetheless, it is the polymorphism in codon 158 (Val158Met) of the gene that codes for catecholamine-O-methyltransferase (COMT) enzyme the most studied in pain conditions. It seems that COMT activity regulates pain nociception and current evidence suggests that the observed association between COMT genotype and pain is unlikely to be epiphenomenal.

It has been reported that genetic polymorphism due to a G→A substitution at codon 158 of the COMT gene leads to a Val to Met substitution and results in different gene activity. The presence of a Val allele results in high enzymatic activity whereas the presence of a Met al lele results in low enzymatic activity. It is accepted that subjects with the Val/Val genotype (LPS, haplotype) exhibit reduced pain sensitivity than those with the Met/Met genotype (HPS haplotype) suggesting that this genotype predisposes for pain and that genetic variability in the gene encoding Val158Met can be important for development of hyperalgesia [129].

Diatchenko *et al.* found that the presence of LPS haplotype (Val/Val) in the COMT gene diminished, by as much as 2.3 times, the risk of developing myofascial TMD [130]. These findings were also supported by the Smith *et al.* within the OPPERA study where the HPS haplotype (Met/Met) was significantly associated with a higher risk (OR: 1.3) of myofascial relative to the other haplotypes [131]. A recent study extended the number of single nucleotide polymorphisms of the COMT gene that could play a regulatory role in TMD susceptibility [132]. In fact, the association between Val158Met polymorphism of the COMT and myofascial TMD was not associated with the presence of depression and anxiety [82]. However, Smith *et al.* also observed that no single-nucleotide polymorphism was significantly associated with myofascial TMD after correction for multiple testing, supporting a contribution from several candidate genes including the COMT or glucocorticoid receptor (NR3C1) among others [131]. Nevertheless, in a more recent study investigating the role of 23 genes, the same authors reported that no genetic markers predicted TMD onset, nonetheless several genetic risk factors for clinical, psychological, and sensory phenotypes associated with TMD onset were observed revealing that myofascial TMD is a complex disease where the use of intermediate phenotypes may reveal new associated genetic pathways [133].

Other genes associated with myofascial TMD are polymorphisms influencing beta-2 adrenergic receptor (ADRβ2) mediated responses [134] or serotonin transporter (5HTTLPR) [135]. It seems that genetics of myofascial TMD are highly complex and future studies are needed. In fact, new genome sequencing technologies will improve individual risk assessment, which will lead to disease prevention or at least early diagnosis and more tailored treatments for patients with myofascial TMD, preventing acute symptoms from becoming chronic [136].

MANAGEMENT

Clinical and scientific evidence demonstrate that proper management of patients with myofascial TMD must be multimodal including several health care professionals, e.g., dentists, orthodontists, medical doctors, physical therapists, and psychologists. In fact, proper therapeutic interventions should see things from a personalized patient's point of view including proper passive and active strategies, active listening, empathy, and addressing psycho-social issues, i.e., depression, anxiety, and catastrophizing, based on clinical findings during the history and examination. Patient-centered care involves shared decision making with mutual respect between clinicians and individuals. Educating the patient about their problems, including the disease mechanism explained in lay person language, is an important part of compassionate care.

Previous studies have demonstrated the role of sensitization mechanisms in the clinical picture and prognosis of myofascial TMD. In fact, the study by Pfau *et al.* found that TMD patients might be divided into 2 main subgroups [60]: one group of patients showing central sensitization (sensitive patients) and a second group exhibiting more peripheral sensitization (non-sensitive patients). This classification agrees with current literature supporting that clinical identification of this sensitization is extremely important since the presence of central sensitization can constitute a poorer prognosis factor for proper physical therapy [137] and also determines treatment parameters, e.g. intensity, amplitude and frequency of the techniques [138]. In fact, the presence of central sensitization in individuals with TMD implies an increased complexity of the clinical reasoning process [139]. Therefore, the challenge facing clinicians is how to select proper treatment approaches for each patient with myofascial TMD, who is likely to be somewhat different in their individual clinical presentations. For choosing the proper multimodal therapeutic approach, consideration must be given to determine if the clinical pattern of the patient has a peripheral input or central input dominance (Table **1**). Further, clinicians should consider potential neurophysiologic and tissue mechanisms underlying the effects (positive and negative) of any intervention that they will apply on each patient. This is particularly important in those patients with chronic pain since it is helpful to encourage patients to choose among various treatment options after proper explanation of the benefits and risks of each therapeutic approach. Asking the patient to participate in decision processes allows them to take responsibility for the management of their condition.

If a clinician identifies that a patient with myofascial TMD seems to be mediated by peripheral nociception (peripheral sensitization), specific treatment of the affected tissue and application of exercises and functional activities should be encouraged. For instance, in a patient where the pain is mostly located in the teeth after a muscle overload, proper treatment of surrounding affected tissues can be cru-

cial for prevent chronification of the symptoms. If a clinician identifies that the patient with myofascial TMD pain seems to be mainly mediated by a central nociceptive processing (central sensitization), a multimodal pharmacological, physical and cognitive approach should be encouraged. In these cases, patients should be also educated on optimizing normal functional movements and undertaking active and specific exercises, in combination with proper passive manual therapies.

It is important to note that patients with central sensitization can exhibit an abnormal pain threshold response to exercise since exercise usually exerts exercise-related hypoalgesia by activating the descending inhibitory pain mechanisms. In individuals with orofacial pain exhibiting central sensitization, this situation is the opposite, exercise induces hyperalgesia [140]. It is important to assess these exercise-induced mechanisms, since activation of descending inhibitory pathways will be extremely helpfully during the treatment process of patients with myofascial TMD.

We will review the most updated evidence for the different therapeutic options for the management of patients with myofascial TMD. List and Axelsson analyzed the evidence regarding management of TMD pain and found 23 qualitative systematic reviews and 7 meta-analyses including reviews on occlusal appliances or adjustment or bruxism, physical therapy, pharmacological drug treatment, surgery; and behavioral therapy and multimodal treatment [141]. This review of reviews concluded that there is some evidence supporting the use of occlusal appliances, acupuncture, behavioral therapy, exercises, and some pharmacological treatment for the management of TMD pain. Evidence for the effect of electrophysical modalities and surgery is insufficient, and occlusal adjustment seems to have no effect and should be avoided [141]. Table **2** summarizes scientific evidence of therapeutic strategies applied on subjects with myofascial TMD pain.

MANUAL THERAPIES

Several manual therapies are clinically advocated to be effective for the management of myofascial TMD. For in-

Table 2. Scientific Recommendations for Potential Treatment Approaches in Patients with Myofascial Temporomandibular Pain (TMD).

Manual therapies including exercises	
Joint mobilizations	Level 1a (systematic reviews). Potential positive results of multimodal manual therapy programs combined with exercises based on low quality studies
Trigger points soft tissue techniques	
Cervical spine treatment	
Postural corrections	
Exercises	
Other physical therapy modalities	
Shortwave diathermy	No evidence available
Therapeutic ultrasound	No evidence available
Low level laser	Level 1a (meta-analysis). Positive and moderate clinical effects
Psychological approaches	
Cognitive-behavioral therapy	Level 1a (systematic reviews and meta-analysis). Potential positive results of different psychological approaches, but based on a limited number of high quality studies
Education	
Biofeedback	
Relaxation training	
Stress management	
Needling therapies	
Acupuncture	Level 1a (meta-analysis). Positive and large clinical effects, but at short-term
Botulinum toxin type A	Level 1b (randomized clinical trial). No significant effects based on one study
Dry needling	Level 1a (meta-analysis). Positive and moderate clinical effects, but at short-term
Orthopedics	
Stabilization splints	Level 1a (systematic review). Limited evidence of efficacy
Hard stabilization appliance	Level 1a (meta-analysis). Limited evidence of efficacy

stance, joint mobilization targeted mandibular accessory ligaments [142], (Fig. **2**) manual therapies aimed to muscle tissues, i.e., myofascial trigger points [18] (Fig. **3**), mobilization interventions targeting the cervical spine [143] (Fig. **4**), or postural correction are applied by many clinicians for the management of TMD pain, even though further studies are clearly needed to assess their efficacy [144].

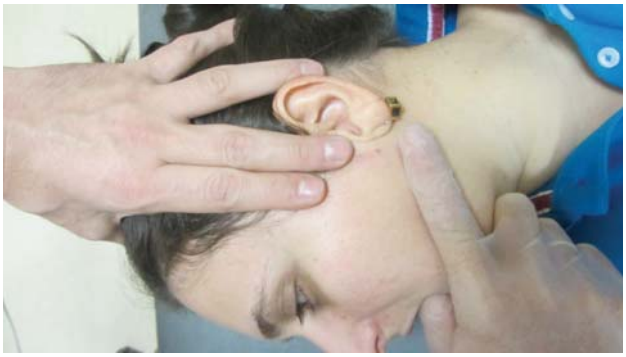

Fig. (2). Joint mobilization of the temporomandibular joint.

Fig. (3). Manual soft tissue therapy applied on the masseter muscle.

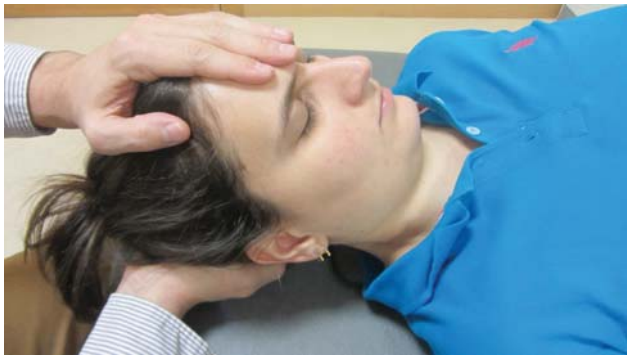

Fig. (4). Posterior-anterior joint mobilization of the cervical spine.

In fact, scientific evidence from systematic reviews on manual therapies is lacking. McNeely *et al.* found that that there are few studies investigating the effectiveness of manual therapies for the management of TMD, in addition that the methodological quality of these studies was poor [145]. This review concluded that the use of manual therapies combined with active exercises maybe effective for reducing pain and improving function in TMD, although more high quality studies are needed [145]. Another systematic review including 30 studies concluded that active exercises combined with manual mobilizations may be effective for treatment of TMD pain and that postural training may be used in combination with other interventions [146]. Again, authors from this review pointed out for the low methodological quality of the studies [146].

EXERCISES

Therapeutic exercise interventions are prescribed to address specific TMJ impairments and to improve the function of the cranio-cervico-mandibular system. Most exercise programs are designed to improve muscle coordination, relax clinically tense musculature, increase range of motion, and increase muscular strength proprioception (force-generating capacity).

Although reports and clinical experience suggest that active exercises can be effective for TMD pain, scientific evidence for this approach is limited since therapeutic exercises are not applied alone, but in association with other conservative procedures [147, 148]. Additionally, several aspects of therapeutic exercise programs need to be clarified: intensity, repetition, frequency and duration.

OTHER PHYSICAL THERAPY MODALITIES

Several electro-physical modalities, e.g., shortwave diathermy, ultrasound, or laser, are also commonly applied in clinical setting. The objective of these electro-physical modalities is to reduce inflammation, promote muscular relaxation, and increase blood flow by altering capillary permeability. Nevertheless, scientific evidence is conflicting. McNeely *et al.* found no evidence to support the use of any electrophysical modality to reduce pain in TMD [145]. On the contrary, a recent meta-analysis observed moderate effect (pooled effect size -0.6) for the application of low-level laser therapy (dosages and treatments with wavelengths of 780 and 830 nm) on the masticatory muscles or joint capsule for TMD pain [149]. Future studies integrating the application of electro-physical modalities within a multidisciplinary treatment program are needed.

PSYCHOLOGICAL APPROACHES

The difficulty in long-term management of a patient with myofascial TMD often lies in the complex task of changing the attitudes, lifestyles, and social and physical environment of the individual. This hypothesis is based on the premise that pain is potentially influenced by inappropriate cognitions, emotions, and behaviors including catastrophizing, hyper-vigilance, avoidance behavior, and somatization. As we previously pointed out, individuals with myofascial TMD exhibit some or all of these psychological problems. It is clear that pain neurophysiology education aiming at conceptualizing pain should be included in the initial phase of treatment in individuals who have inappropriate beliefs about their pain symptoms and complaints. If not, a poor

understanding of their pain may lead to the acquisition of maladaptive attitudes, cognitions and behavior and a consequent poor compliance to any active exercise program.

Several psychological approaches can be applied on patients with myofascial TMD. For instance, cognitive-behavioral therapy for chronic pain seems to be successful at reducing pain catastrophizing and improving pain intensity and physical and psychosocial disability [150]. In their review of systematic reviews, List & Axelsson concluded that education, biofeedback, relaxation training, stress management, and cognitive-behavioral therapy were effective in the management of TMD [141]. A meta-analysis has confirmed that application of psychological interventions trend toward greater improvements of psychological outcomes, but not physical outcomes, in patients with myofascial TMD; however, no evidence was found to distinguish the clinical effectiveness between usual treatment and psychosocial interventions [151]. It is clear that psychological and cognitive approaches should be integrated within a multidisciplinary treatment program including physical and rehabilitation interventions.

NEEDLING THERAPIES

Different needling therapies are also generally applied by clinicians in individuals with TMD pain: acupuncture, dry needling and botulinum toxin type A. A meta-analysis concluded that acupuncture is more effective than placebo in reducing pain intensity in TMD (pooled standardized mean difference 0.83; 95%CI 0.41-1.25) at short term [152]. Another meta-analysis concluded that trigger point dry needling exhibited grade A evidence for reducing pain in upper quadrant syndromes, including myofascial TMD pain, at short-term [153]. Finally, the efficacy of Botulinum toxin type A in patients with myofascial TMD pain is questioned [154].

ORTHOPEDICS

Application of different orthopedic approaches have been claimed to be clinically effective for the management of TMD pain. In their review of reviews, List & Axelsson has concluded that management of TMD with a stabilization splints worn at night is likely to lead to short-term improvements when compared with no treatment, but the effects compared with placebo (non-occluding palatinal splint) is inconclusive [141].

Fricton *et al.* found that hard stabilization appliance improved TMD pain compared to non-occluding appliance (pooled effect size 2.46, 95%CI 1.56-3.67) and no-treatment control (pooled effect size 2.15, 95%CI 0.80-5.75), although the latest one did not reach statistically significance [155]. Other types of appliances, including soft stabilization appliances, anterior positioning appliances, and anterior bite appliances exhibited limited evidence of efficacy [155]. A recent meta-analysis concluded that splint therapy was effective more reducing pain in TMD (mean response -0.93, 95%CI -1.33 to -0.53); however evidence was moderate due to the bias of the included trials [156]. Therefore, although overall scientific evidence is somewhat promising, establishing the role of splints for patients with TMDs will require large trials with stronger safeguards against bias.

CONCLUSION

The current paper has summarized updated data on epidemiology, clinical features, differential diagnosis, pathophysiology, and management related to subjects suffering from myofascial TMD-related pain. Current data suggests that myofascial TMD pain is a complex pain disorder where multiple factors are involved. Proper therapeutic management of these patients should be personalized and based on clinical findings and personal attitudes including techniques targeting both physical and psychological impairments.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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