Referred Pain in Temporomandibular Disorders: Prevalence, Associated Factors and Effects on TMD Prognosis

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Abstract

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When a stimulus is applied to one part of the body, pain sometimes occurs in a distant site. This distant pain is called referred pain. The *aims of this project were*: To describe the prevalence of referred pain in subjects with temporomandibular disorders (TMD) at baseline and 8-year follow-up and the prevalence of persistence of referred pain at follow-up. Another aim was to identify risk factors for having referred pain at baseline and for predicting its persistence at follow-up. Finally, we wanted to determine whether referred pain affects the prognosis of patients with a TMD diagnosis. For each objective, we explored demographics such as gender, age, income, education level, and race. Other factors investigated included facial pain duration, somatization, somatization without pain, depression, anxiety, characteristic pain intensity (CPI), graded chronic pain scale (GCPS), number of other pains (headache, chest, back or stomach), and TMD diagnosis (myofascial pain, disk displacement, arthralgia or degenerative joint disease DJD). *Methods*: This secondary analysis included the data sets from the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Validation (baseline) and IMPACT (follow-up) studies. It focused on a subclassification pain diagnosis termed "myofascial pain with referral". Subjects included in our analysis were TMD cases at baseline (n = 614) and TMD cases at follow-up (n = 286). *Results*. 26.4% of TMD cases had pain with referral at baseline and 36.4% at follow-up. The sites most likely to refer pain were extraoral sites (temporalis, masseter and mandible) at both baseline and follow-up. Female gender was associated with a higher

prevalence of referred pain at baseline (p=.025). Other factors associated with referred pain included somatization (p<.0001 at baseline, p=.0195 at follow-up) and somatization without pain at baseline only (p<.0001), depression (p=.001 at baseline and p=.0002 at follow-up), CPI, GCPS and number of other bodily pains were also associated with referred pain at baseline and follow-up (p<.0001). Myofascial pain and arthralgia or DJD were TMD diagnoses associated with referred pain at baseline and follow-up (p<.0001). The rate of persistence from baseline to follow-up was 57.4%, with CPI being the only predictor of persistence (p=.02). On the impact on prognosis of TMD condition, regression analyses determined that referred pain was a predictor of CPI (p=.028) and moderate depression at follow-up (p=.028). *Conclusion*: Among individuals with TMD, referred pain was observed in around 30% at baseline and follow-up and persisted from baseline to follow-up in more than half of the individuals. It can be detected by following the protocol used by RDC/TMD and further revised by DC/TMD. It is associated with self-reported measures of both psychosocial factors and subjective pain measures that are associated with central sensitization process. Referred pain is an added and an independent factor for higher CPI and therefore may predict an overall higher intensity of pain and suffering. Referred pain is an important marker for assessment and management of any orofacial pain condition. In addition to indicating an increased central sensitivity, it may also reveal the true pain source in a pain condition that has otherwise been misdiagnosed

Acknowledgment

To my future self: “Reflect your power of will, witness a change, make an impact, impart knowledge to colleagues, inspire your students, motivate your society to demand and take action, speak out loud, never remain silent, and never give up on your dreams”.

I dedicate this work to my family, my parents, brothers, sister in law and niece, thank for your support all along and for understanding my lengthy journey. Sorry for not being around, sorry it took me so long to figure out how to create myself.

I would like to acknowledge all my committee members: Dr. LeResche, Dr. Mancl, and Dr. Heaton thank you for your support and guidance on this project. I would like to express a special gratitude to my mentor Dr. Truelove who inspired me to attain my fullest potential as a researcher and a clinician. I would also like to extend my appreciation to everyone in the Department of Oral Medicine: faculty, fellow residents and staff for making this place feel like home to me along with enhancing my experience.

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Introduction

Referred Pain: Definition and Pathogenesis

When a stimulus is applied to one part of the body, pain sometimes occurs in a distant site. This distant pain is called referred pain, which is a phenomenon of nociceptive alteration. Referred pain has also been identified as “heterotopic pain” and/or “secondary hyperalgesia”(Okeson 2005). Similar to other nociceptive changes such as hyperalgesia “an increased response to a stimulus that is normally painful” (Loeser 2001) or allodynia “pain produced by a stimulus that does not normally cause pain” (Loeser 2001), referred pain can change character over time (Okeson 2005). In the literature, referred pain from muscles has been commonly defined as “Pain elicited in regions remote from the site of palpation”; this has been attributed to the presence of trigger points (TrPs) (Travell and Simons 1983). The Diagnostic Criteria for Temporomandibular Disorder (DC/TMD) has established valid and reliable operational definitions to identify referred pain clinically. “Myofascial pain with referral” was defined as familiar pain elicited from a muscle source that spreads to an anatomically distinct muscle or structure that is not necessarily identified as a familiar component by the patient (Schiffman et al. 2014).

Trigger points are clinically defined as the site of origin of pain that arises in a completely remote area “trigger zone” away from the active locus. Trigger points have been shown experimentally to produce spontaneous electrical activity in both animal and human models (Hubbard and Berkoff 1993, Simons et al. 1995). The pain that arises is usually not dependent on the distribution of peripheral nerve nor the dermatomal or myotomal segment (Travell and Simons 1983, Sharav and Benoliel 2008). In a broader definition of referred phenomena arising from trigger points, Travell and Simons (1983) stated that both sensory and motor phenomena such as pain, muscle hyperactivity, vasoconstriction or vasodilation as well as hypersecretions of both lacrimal and salivary glands are signs and symptoms that can also manifest at a distance from the site of origin of the primary trigger point (Travell and Simons 1983). Symptomatically, a trigger point can either be “active” or “latent”. A TrP is considered active if it produces a clinical complaint (usually pain) at the palpated site that the patient is familiar with when the TrP is digitally compressed. An active TrP may also be the site of spontaneous pain or headaches. A latent TrP may produce pain only upon applying an excessive amount of pressure, but its main feature is restriction and stiffness in muscle range of

motion. Both active and latent TrPs may have similar physical and clinical criteria and conversion from latent to an active state is thought to be possible but not the other way around (Travell and Simons 1983). “SatelliteTrPs” are TrPs that can arise in the reference zone due to an indirect influence from the source TrP referring pain (Travell and Simons 1983). Other factors such as joint dysfunction, emotional distress as well as some overload of secondary visceral pain such as pain due to a peptic ulcer was also thought to increase the likelihood of TrP activation (Travell and Simons 1983). Direct activation of TrPs however, has been controversial in the sense that it has been associated with physical initiating factors such as acute overload, overwork fatigue, direct impact trauma, and radiculopathy. These factors are mentioned in the literature on physical rehabilitation and myofascial pain syndrome, describing not only the TrP activation theory but also how TrPs can further embed within a tangible taut band (Travell and Simons 1983, Fricton et al. 1985).

Referred Pain: Pathophysiology and Mechanisms

Similar to its definition and clinical identification, the pathophysiology of referred pain is also controversial (Smith et al. 2011). Although it has been shown that referred pain is a centrally mediated phenomenon, a localized peripheral level of sensitization mechanism is still evident (Woolf 2011, Fernandez-de-las-Penas and Dommerholt 2014). It is thought that structures like interneurons and the reticular formation present on the spinothalamic tract are responsible for conveying motor reflexes that in turn act as mediators for convergence of pain inputs to the main sensory ganglion (Hu and Sessle 1988, Sessle 2000). Therefore, pain can travel from one nerve division to another, crossing its identified receptive field territory (Saxon and Hopkins 1998). In other words, once the peripheral nociceptors from either somatic or visceral origin converge on a single projection neuron in the dorsal horn, higher levels of the CNS (structures like interneurons and reticular formation) cannot distinguish the source of the signal input and attribute the sensation to somatic structures by default because somatic sensory representation predominates in the CNS (Griffen 2001,p.99)

The theory of integration of central and peripheral mechanisms, however, states that peripheral sensitization is considered an integral part in the development of referred pain from a trigger point (Fernandez-de-las-Penas and Dommerholt 2014). Referred pain areas with pressure hyperalgesia were provoked by injecting painful glutamate in latent trigger points in healthy patients, compared to non-myofascial trigger points in the same individuals (Wang et al. 2012). The finding

supports the concept that trigger points in Myofascial Pain Syndrome (MPS) are locally sensitized and therefore contribute to the induction of spatial pain propagation (Wang et al. 2012). This previous study and other similar experimental trials that provoke localized and referred pain from peripheral trigger points suggest an integration of both peripheral and central mechanisms in the development of referred pain (Svensson et al. 2003). The spontaneous electrical activity that is evidential of TrPs represents a focal muscle contraction within the taut band. This local twitch response (LTR) arising from the extrafusal motor endplate represents a dysfunctional motor control strategy (Ge et al. 2011). In 1993, a clinical study reported the presence of hyperactivity upon measuring resting amplitudes during advancement of a needle EMG in a 1 mm area of an active TrP located in trapezius muscles of patients diagnosed with a tension headache (Hubbard and Berkoff 1993). Later on, Simons and Hong reported similar experimental finding in muscle TrPs in rabbits (Simons et al. 1995).

Referred Pain: Diagnosis and Characterization

Clinical researchers and physicians have been attempting to clinically validate criteria that would ensure the reliability and validity of identifying trigger points, regardless of the poor understanding of their pathophysiologic background and clinical implications. Two different methods have been utilized to identify referred pain: either through identifying TrPs and their theoretical association with a physical sign called “taut band”, or through experimental injection, usually of hypertonic saline, followed by identifying the large area in which pain is propagated and/or traveled.

Taut bands are a physical fibrous finding embedded along the long fibers of skeletal muscles. Historically, these bands were thought to be the cause of primary restriction in muscle capacity. Attempts to extend the muscle and stressing it was said to cause secondary muscle pain (Travell and Simons 1983). Upon close examination of these bands clinically and in research, it has been found that compression of these knots may initiate the so-called local twitch response (LTR) due to a reflex contraction of these muscles. Travell and Simons in the late 1970s reidentified taut bands as a group of tense muscle fibers extending from a trigger point to the muscle attachment. In their definition, they implied that taut bands are developed secondary to the existence of myofascial TrPs due to the tension that is caused by the intense stimulation and consistent contraction of the trigger point areas (Travell and Simons 1983). Therefore, a tender nodule/ a taut band /a tender knot or spot has always been a characteristic and the main finding of a TrP. Fricton et al (1985) developed diagnostic criteria

for myofascial pain syndrome in the orofacial region and attempted to characterize referred pain zones and the corresponding active trigger point's anatomic location, in addition to attempting to standardize a proper palpation technique as well as physical consequences ("a headache" and/or behavioral reaction "jump sign").

The first attempt to measure the sensitivity of trigger points was established using a pressure algometer (Fischer 1986). However, in 1989, Ohrbach and Gale discovered that referred pain was provoked similarly in characterized taut bands as well as unremarkable spots in subjects with masticatory muscle pain, by using a pressure algometer (Ohrbach and Gale 1989). Fricton et al (Fricton 1993) established reliability for the diagnosis of myofascial pain syndrome, but it was not until 1997 that Gerwin et al was able to establish good results for inter-rater reliability for the purpose of clinical standardized evaluation of trigger points in five different muscles (Gerwin et al. 1997). The study looked at the most commonly identified clinical characteristics: Tangible taut band, local twitch response (LTR), referred pain "in response to applying 20 Newtons of force for 5 seconds compressing the trigger point", production of usual pain, restricted range of motion, weakness without atrophy and autonomic symptoms. Gerwin et al attempted to look at the reliability of the trigger point exam with a two-part study. The first phase (prior to extensive training) failed to establish inter-rater reliability, the second phase, however, successfully identified some characteristics that had high Kappa coefficients among the same examiners. The agreement among examiners at the second phase seemed to be attributed to the training session that was delivered prior to the second attempt (Gerwin et al. 1997). Substantial agreement was found for referred pain and reproduced pain for each muscle (sternocleidomastoid: 95%; trapezius: 93%; Infraspinatus: 89%; latissimus dorsi: 95%; extensor digitorum: 100%). The kappa coefficient (S_{av}) was high for all muscles $p<.001$ (S_{av} of 0.6 and above) (Gerwin et al. 1997).

In an updated review in 1996 (Simons 1996), Simons stated that identifying a tangible taut band to diagnose myofascial pain syndrome MPS is ambiguous because tender taut bands might be found in normal subjects. However, the association of the distinguishable spot tenderness within the taut band would likely provide good discrimination and with proper training might qualify as a reliable diagnositic criterion (Simons 1996). Referred pain is a difficult sign to obtain from a taut band with spot tenderness, and therefore is a less discriminative diagnostic sign for trigger points. A local twitch response that can be elicited on a taut band either during manual palpation or needling is evidently

the best criterion to distinguish active TrPs (Simons 1996).

In the craniofacial area, physicians and dentists are mostly interested in Temporomandibular Pain Dysfunction/Disorder, where the pain is mainly manifested in primary as well as supplementary masticatory muscles. Clinicians were seeking validated criteria to distinguish myofascial pain from a pain that might be secondary to intradiscal derangement (Fricton et al. 1985, Fricton and Schiffman 1986) A method to palpate muscles and a full palpation index was developed to validate a craniomandibular index (Fricton and Schiffman 1986). The palpation method was described as the following:

"Palpation is performed by first locating the distinct muscle band or part of joint and then palpating using the sensitive spade-like pad at the end of the distal phalanx of the index finger using firm pressure (approximately 1 lb. per square inch). The patient is asked, "Does it hurt or is it just pressure?" The response is positive if palpation produces a clear reaction from the patient: i.e., palpebral response, or if patient stated that the palpation "hurt", indicating that the site was clearly more tender than surrounding structures or contralateral structures " (Fricton and Schiffman 1986).

Later came the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) (Dworkin 1992) and the separate TMD validation study (Schiffman et al. 2010) that did not focus on referred pain per se, but rather attempted to validate the main subclasses of the common signs and symptoms of TMD. According to the most recent DC/TMD criteria (Schiffman et al. 2014) that included referred pain as part of an extended nomenclature, to diagnose myofascial pain with referral, the clinician must clinically confirm the site of pain first then apply 1-2 Lbs of pressure for 5 seconds. The patient then must report familiar pain at the site of the palpation then localize the referred pain zone located outside the boundary of that structure. According to this definition, the palpated site does not need to meet the definition of a trigger point.

As far as experimental injection methods, Alonso-Blanco et al have utilized the Center of Gravity (COG) method to localize referred pain areas elicited by experimental injection of a hypertonic solution to active trigger points in patients with myofascial pain (Cristina Alonso-Blanco et al. 2012). Referred pain was defined as pain located at least 1 cm outside the local pain area provoked by palpation, and the elicited pain was familiar to the participant. This technique and protocol were initially utilized by Svensson et al (Svensson et al. 2003).

Referred Pain: Clinical Characteristics

Patients with active myofascial TrPs usually have poorly localized dull aching pain that may involve the whole muscle and extend to an associated joint (Fricton et al. 1985, R Gerwin et al. 1997). Symptoms of paraesthesia and numbness may also accompany pain referrals (Travell and Simons 1983). TrPs may cause a disturbance in autonomic function such as sweating, sustained salivation and lacrimation. Related proprioceptive disturbances such as dizziness, imbalance, or tinnitus as well as distorted weight perception of objects may be also associated with TrPs (Travell and Simons 1983). Loss of muscle coordination decreased workload and tolerance may affect muscles associated with TrPs (Travell and Simons 1983).

Experimental studies showed a higher prevalence of referred pain in females (Svensson et al. 2003, Schmidt-Hansen et al. 2007). Experimental injection of hypertonic saline produced a greater intensity of pain and greater areas of referred pain among females with a tension-type headache compared to males (Schmidt-Hansen et al. 2007). Similarly, glutamate injection of masseter muscles produced higher intensity, larger pain areas and longer pain duration in females compared to males (Svensson et al. 2003)

The intensity and extent of the referred pain pattern are thought to be dependent on internal factors within the TrP itself, not on the size of the muscle nor its location (Travell and Simons 1983).

In an attempt to understand the referred pain phenomenon, clinical studies have been exploring its prevalence, characteristics, associated symptoms as well as its possible prognosis. In a cross-sectional study of 296 subjects diagnosed with myofascial pain syndrome of the head and neck, 55.5% of the sample had referred pain in the TMJ (Fricton et al. 1985) This was produced mostly by palpating active trigger points located in the deep masseter, intermediate/deep temporalis, lateral/medial pterygoid and digastric muscle groups. Two-thirds (63.4%) of subjects had referred pain to the orofacial area that was generated from trigger points located in the superficial masseter, trapezius, and digastric and medial pterygoid muscle groups. Another cross-sectional study that utilized the COG method by Alonso-Blanco and colleagues 2011 found that trigger point prevalence and anatomic location of referred pain areas in the head and neck musculature differ between adults and children with chronic tension-type headache (CTTH). The study also concluded that an increased number of trigger points was associated with longer headache duration and higher intensity in patients diagnosed with CTTH (Alonso-Blanco et al. 2011).

From of the available literature in orofacial pain, another cross-sectional study by Alonso – Blanco et al (2012) attempted to characterize and identify the anatomic location of trigger points that refer pain to the head in women with myofascial TMD pain compared to women with fibromyalgia (Alonso-Blanco et al. 2012). The results showed that there are more trigger points located in masticatory muscles compared to neck muscle structures in fibromyalgia patients (Alonso-Blanco et al. 2012). In a case-control blinded study, multiple trigger points existed in masticatory and neck-shoulder muscles in women with myofascial pain compared to age-matched healthy controls with no pain. Local and referred pain elicited from manual palpation of active trigger points replicated the pattern of clinical pain in TMD subjects. In addition, this study further characterized the referred pain zones, surface area, number of active and latent trigger points as well as qualifying the type of pain that was provoked (Fernández-de-las-Peñas et al. 2010).

Referred Pain: Prevalence, Course, and Prognosis

To our knowledge, there are few clinical studies that attempted to quantify and map referred pain under defined criteria in the orofacial area. In 2014, a large clinical cross-sectional study found that the most common palpation sites eliciting referred pain in patients diagnosed with TMD based on RDC/TMD criteria were located within the masseter muscle (34.2%) and temporalis (18.7%) (Sanches et al. 2014). The study also recorded referred pain zones and suggested a topographic and anatomic division of the head and neck muscles for a universal reproducible use of the proposed mapping (Sanches et al. 2014)

Following on the prognosis of chronic pain, in general, we find that the predicting factors for chronicity and poor prognosis are consistent within all pain models. In the lower back pain model, a prospective cohort study investigated multiple demographic, social, physical and psychological factors and found that higher pain intensity scores at baseline and higher scores of kinesophobia were associated with disability over a period of 3 years (Heymans et al. 2010). Pressure pain threshold (PPT) a widely accepted measure of central sensitization was shown to impact subjective pain intensity (Vedolin et al. 2009). Local muscle pain intensity, stress, and anxiety have also shown to impact PPT in patients with myofascial pain of masticatory muscles (Vedolin et al. 2009).

Referred pain may contribute to the transition from localized pain to widespread pain via enhanced peripheral and central sensitization as shown experimentally (Ge et al. 2011). This course

is consistent with the model of predicting chronic TMD proposed by Epker et al (Epker et al. 1999), a longitudinal-cohort design where 204 patient diagnosed with TMD based on RDC/TMD were grouped into either chronic or non-chronic. The subjects were evaluated via an assessment battery that included physical and psychosocial measures. The combined model was able to detect the development of chronic TMD in 91% of subjects with acute TMD. The two variables that were statistically relevant predictors were characteristic pain intensity and Myofascial pain diagnosis (Epker et al. 1999).

Objectives

The overall goal of this study was to assess the prevalence of and risk factors associated with referred pain from the masticatory muscles, both cross-sectionally and longitudinally. We determined three specific objectives based on the analyses of the existing data set. The first objective was to describe the prevalence of referred pain in subjects with TMD at baseline and the prevalence of persistence of referred pain at 8-year follow-up. The second objective was to identify risk factors for having referred pain at baseline and factors that would predict its persistence at follow-up. Finally, we wanted to determine whether referred pain affects the prognosis of patients with a TMD diagnosis. For each objective, we explored demographics such as gender, age, income, education level, and race. We investigated variables that may be associated with the risk of having referred pain at baseline and follow up, or might serve as a predicting factor for persistence at follow-up or poor TMD prognosis. These variables included: facial pain duration, somatization, somatization without pain, depression, anxiety, characteristic pain intensity (CPI) and graded chronic pain scale (GCPS) in the past 6 months, number of other pains (headache, chest, back or stomach) as well as TMD diagnosis (myofascial pain, disk displacement, arthralgia or DJD).

Hypotheses

Parallel to our study objectives we first hypothesized that:

1) Referred pain arising in the muscles of mastication and TMJ is common in patients with TMD and may continue to persist along the temporal chronicity of the illness.
2) Patients with TMD have variable probability of having referred pain, dependent on specific risk factors. We predicted that these factors would be biopsychosocial variables. This

hypothesis relies on the integration of the biopsychosocial model and central sensitization, with the psychosocial factors being the expression of the process of central sensitization and the up-down regulation of pain. Measures such as high GCPS, (encompassing high CPI and high levels of disability) as well as increased somatization with or without pain, anxiety, depression, and number of other pain conditions are psychosocial factors associated with chronicity of pain and therefore with central sensitization.

3) We hypothesized that referred pain would predict poor prognosis of TMD. If our hypothesis was true it then means that referred pain would be associated with increased somatization, depression and anxiety scores as well as increased number of other pain conditions and an advanced graded chronic pain score (GCPS). Although prior studies did not identify referred pain as we did, we based these hypotheses on available literature on myofascial pain syndrome (MPS).

Methods

Data were collected from: the cross-sectional RDC/TMD Validation study (Schiffman et al. 2010), as well as the 8 year follow-up IMPACT study (Schiffman et al. 2014), where the target condition was Temporomandibular Disorders (TMD) as defined by the US National Institute of Dental and Craniofacial Research (NIDCR). The aim of the validation study was to infer reliable and valid revised Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) for both Axis I and II diagnostic system. The validation project determined that the Axis I validity of clinical diagnostic algorithms was below the target sensitivity of ≥ 0.7 and specificity of ≥ 0.95. The project proposed modifications of this protocol that would improve its reliability and validity as a taxonomic system; ongoing cooperation to investigate its validity was highly recommended. Two international consensus workshops were held, from which recommendations were obtained from the finalization of a new Axis I clinical diagnostic algorithms and new Axis II instruments (Schiffman et al. 2014).

The Validation and IMPACT studies were multisite collaborations among researchers at the University of Minnesota (UM), the University of Washington (UW) and the University at Buffalo (UB). Recruitment for baseline took place between August 2003 and September 2006. All data were collected prospectively following the Standards for Reporting of Diagnostic Accuracy (STARD) (McShane et al. 2006). Cases with a full spectrum of TMD signs and symptoms were selectively

recruited to fulfill some of the less common diagnostic categories of intradiscal subgroups. Older-aged participants were also selectively recruited for the purpose of completion of Axis II assessment. The study sample was a convenience sample in which participants were either selected through direct referrals from local health care providers to the university-based TMD centers or through community advertisements (Schiffman et al. 2010). Also, the data from follow-up was utilized for field-testing and establishing an inter-examiner reliability for Axis I and II of the refined diagnostic criteria DC/TMD(Schiffman et al. 2014) that took place between 2011-2012. The participants were aged between 18 to 70 years old and were enrolled as either TMD cases or controls based on specific inclusion and exclusion criteria. For TMD cases, participants qualified if they reported the presence of at least one of the three cardinal signs and symptoms of TMD: Jaw pain, limited mouth opening, or TMJ noise. Study exclusion criteria were:

I. History

   Systemic rheumatic, neurogenic/neuropathic, endocrine, or immune/autoimmune disease or widespread pain.

   Radiation treatment to head and neck.

   TMJ surgery.

   Trauma to jaw in the last 2 months.

   Presence of non-TMD orofacial pain disorders.

   Pregnancy.

   Unable to participate due to language barrier or mental intellectual disability.

   Use of narcotic pain medication, muscle relaxants or steroid therapy unless discontinued for 1 week prior to examination.

   Use of antidepressant drugs unless the participant has been on a stable dose for 60 days.

   Use of prescription or over-the-counter nonsteroidal anti-inflammatory medications unless the medication(s) were discontinued for 3 days prior to the examination (use of acetaminophen was allowed as a rescue drug).

   Drug abuse.

   Ongoing dental treatment.

   Wearing dentures.

   Contraindications for imaging.

Ongoing TMD treatment unless on a stable regimen for at least 2 months.

Unable or unwilling to give informed consent.

II. Clinical examination

Presence of non-TMD orofacial pain disorders.

III. Imaging

MRI positive for pathology(exception for cases: TMJ disc displacement).

CT is positive for osseous pathology (except for cases: TMJ osteoarthritis).

Panoramic radiograph is positive for osseous (non-TMJ related) or odontogenic lesions.

Tests and measures for the study population included: a) demographic measures (e.g., age (divided into quartiles to establish equal sampling in each age group and to define a certain trend among participants as well as simplifying the comparison upon analyzing different factors), gender, race, education level (categorized as college level, beyond college and some college or less) and income (divided into four categories). b) Baseline measures of clinical characteristics included characteristic pain intensity (CPI) (Dworkin 1990), as well as duration of pain, depression, nonspecific physical symptoms, grade chronic pain scale (GCPS) (Von Korff et al. 1988), and RDC/TMD Axis I diagnosis.

Axis I diagnostic procedure utilizes a set of standardized clinical and questionnaire items, each clinical item has been identified with clear operational criteria that leads to a set of three diagnostic groups and eight subdiagnoses:

- Group I Muscle Disorders: Myofascial pain(Ia); Myofascial pain with limited opening (Ib).
- Group II Disc Displacement: disc displacement with reduction (IIa); disc displacement without reduction with limited opening (IIb); disc displacement without reduction without limited opening (IIc).
- Group III Arthralgia, Arthritis, Arthrosis: arthralgia (IIIa); osteoarthrosis (IIIb); osteoarthritis (IIIc).

The diagnosis of Myofascial pain with referral (Ia.1) was part of the expanded TMD taxonomy of Group I Muscle Disorders from the validation project (Schiffman et al. 2014). The protocol for performing the myofascial palpation test included the following components: palpation of the RDC/TMD muscle palpation sites using a range of 1-2 pounds of pressure applied for 5 seconds using the spade-like pad of a finger. Participants reporting pain were asked if it was familiar (like their pain of complaint) and if the pain was felt at any other site external to the muscle being palpated.

Participants with a report of pain were prompted to indicate if the pain was referred and pinpoint in what other sites it was felt. Referring pain sites were then grouped into extraoral (temporalis, masseter, posterior mandibular i.e, “stylohyoid muscle and digastric muscle” and submandibular, i.e, “medial pterygoid muscle”) intraoral (lateral pterygoid and temporalis tendon) and joint sites(lateral pole and posterior attachment).

Axis II evaluation included self-report questionnaires that were administered to assess pain, mood, pain-related disability, health-related disability, stress reactivity, sleep, and behaviors. The Instruments utilized in our analysis were all previously validated and showed a high reliability, they included: characteristic pain intensity (CPI) (Dworkin 1990) which is the average score of worst, average and current pain intensities. Graded Chronic Pain Scale (Von Korff et al. 1988) which is a 4-grade scale calculated by an algorithm based on CPI, pain-related interference score and number of disability days. Symptom Checklist SCL-90R score for depression, somatization, somatization without pain and anxiety (Derrogatis et al. 1973) are continuous scores categorized as normal, moderate or severe based on the cutoffs described in the RDC/TMD (Dworkin 1992). Other instruments such as Jaw Functional Limitation Scale (Ohrbach et al. 2008), Multidimensional Pain Inventory (Kerns et al. 1985), SF-12 Health Survey (Ware Jr et al. 1996) were part of the primary studies but were not included in the current analysis.

This secondary analysis included the data sets from the RDC/TMD Validation (baseline) and IMPACT (follow-up) studies. It focused on a subclassification pain diagnosis termed “myofascial pain with referral”. Subjects included in our analysis were TMD cases at baseline (n = 614) and TMD cases at follow-up (n = 286). The analysis presented here was restricted to TMD cases. Controls at baseline (n=91) and follow up (n=110) were not included in the analysis. Only one control subject at follow-up had referred pain, and it was only for one palpation site (right lateral pole)

Statistical analysis

The prevalence of referred pain at baseline and follow-up was defined as one or more sites with referred pain based on all palpation sites and by extraoral, intraoral, and joint sites. Extraoral sites (16 sites) were further divided into temporalis (6 sites), masseter (6 sites), and mandibular (4 sites). There were 4 sites each for intraoral and joint sites. The chi-square test and Fisher’s exact test were used to identify demographic and clinical characteristics associated with referred pain at baseline and

referred pain at follow-up. Similar methods were used among subjects with referred pain at baseline to calculate the rate and assess for risk factors for persistent referred pain at follow-up. Regression methods were used to determine if referred pain at baseline was predictive of various clinical characteristics at follow-up after adjusting for the baseline clinical characteristic. Logistic regression was used for binary characteristics (TMD diagnoses), linear regression for quantitative characteristics (CPI), multinomial logistic regression for categorical characteristics (GCPS, somatization and depression categories), and ordinal logistic regression for number of other pain conditions. In addition, regression methods were used to test for an interaction between referred pain and each clinical characteristic at baseline. All analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA.)

Results

Descriptive data

A total of 705 subjects were included in the Validation study (baseline); 614 were TMD cases, the remainder were controls. There were 286 TMD cases at follow-up (IMPACT study). Median (IQR) follow up time was 7.85 (7.3 to 8.3) years. The mean age of the sample at baseline was 36.90 (±13.16) years. Baseline demographics and assessment measures for the TMD cases at baseline and follow-up are shown in Table 1.

Table 1: Characteristics of TMD cases at baseline (n=614) and follow-up (n=286)

Characteristic		*Baseline N(%)*	*Follow-up N (%)*
Gender	*Female*	*523 (85.2%)*	*255 (89.5%)*
	Male	*90 (14.7%)*	*30 (10.5%)*
	No data	*1 (0.2%)*	
Age (years)*	*18 to 24*	*151 (24.6%)*	*76 (27.0%)*
	25 to 35	*155 (25.2%)*	*64 (22.7%)*
	36 to 47	*145 (23.6%)*	*72 (25.5%)*
	48 to 67	*163 (26.5%)*	*70 (24.8%)*
Race	*American Indian/Alaskan Native*	*5 (0.8%)*	*2 (00.7%)*
	Asian	*21 (3.0%)*	*6 (02.1%)*
	None Hispanic/Pacific Islander	*2 (0.3%)*	*1 (00.3%)*
	Black/African American	*12 (2.0%)*	*5 (01.7%)*
	White	*561 (91.4%)*	*265 (92.7%)*
	>1 race	*12 (2.0%)*	*7 (02.4%)*
	No data	*1 (0.2%)*	
Income (dollars)	*No data*	*8 (1.3%)*	

	<10K	*96 (15.6%)*	*18 (7.6%)*
	10-39K	*190 (30.9%)*	*42 (17.6%)*
	40-79K	*196 (31.9%)*	*89 (37.4%)*
	≥ 80K	*124 (20.2%)*	*89 (37.4%)*
Education level	*Some college or less*	*274 (44.6%)*	*88 (31.0%)*
	College	*190 (30.9%)*	*126 (44.4%)*
	Beyond college	*149 (24.3%)*	*70 (24.6%)*
	No data	*1 (0.2%)*	
Recruitment site	*UM*	*177 (28.8%)*	*97 (33.9%)*
	UW	*215 (35.0%)*	*97 (33.9%)*
	UB	*222 (36.2%)*	*92 (32.2%)*
Number of other pains (headache, chest, back or stomach)	*No data*	*2 (0.3%)*	
	0	*88 (14.3%)*	*29 (10.2%)*
	1	*168 (27.4%)*	*72 (25.3%)*
	2	*211 (34.4%)*	*110 (38.6%)*
	3	*106 (17.3%)*	*66 (23.2%)*

	4	*39 (6.4%)*	*8 (2.80%)*
Duration of facial pain (years)	*No pain*	*105 (17.1%)*	
	0 to <2	*113 (18.4%)*	*42 (23.1%)*
	2 to <6	*137 (22.3%)*	*39 (21.4%)*
	6 to <13	*128 (20.8%)*	*52 (28.6%)*
	>13	*131 (21.3%)*	*49 (26.9%)*
Somatization	*No data*	*2 (0.3%)*	
	Normal	*172 (28.0%)*	*71 (24.9%)*
	Moderate	*154 (25.1%)*	*88 (30.9%)*
	Severe	*286 (46.6%)*	*126 (44.2%)*
Somatization without pain	*No data*	*2 (0.3%)*	
	Normal	*436 (71.0%)*	*183 (64.2%)*
	Moderate	*107 (17.4%)*	*63 (22.1%)*
	Severe	*69 (11.2%)*	*39 (13.7%)*
Depression	*No data*	*2 (0.3%)*	
	Normal	*396 (64.5%)*	*178 (62.5%)*

	Moderate	*145 (23.0%)*	*60 (21.1%)*
	Severe	*71 (11.6%)*	*47 (16.5%)*
Anxiety	*No data*	*3 (0.50%)*	
	Normal	*491 (80.0%)*	
	Moderate	*80 (13.0%)*	
	Severe	*40 (6.5%)*	
CPI*	*0*	*112 (18.2%)*	*37 (13.0%)*
	>0 to 40	*159 (25.9%)*	*78 (27.4%)*
	>40 to 60	*188 (30.6%)*	*108 (37.9%)*
	>60	*15 5 (25.2%)*	*62 (21.8%)*
GCPS*	*0*	*116 (18.97%)*	*37 (13.0%)*
	1	*215 (35.0%)*	*198 (69.7%)*
	2a	*155 (25.2%)*	*27 (9.50%)*
	2b	*66 (10.7%)*	*2 (0.70%)*
	3 or 4	*62 (10.1%)*	*20 (7.00%)*
TMD Diagnosis:	*Yes*	*495 (80.6%)*	*76 (26.8%)*

Myofascial pain	*No*	*119 (19.4%)*	*208 (73.2%)*
TMD Diagnosis: Disk displacement	*Yes*	*513 (83.6%)*	*100 (35.2%)*
	No	*101 (16.4%)*	*184 (64.8%)*
TMD Diagnosis: Arthralgia or DJD	*Yes*	*493 (80.3%)*	*67 (23.6%)*
	No	*121 (19.7%)*	*217 (76.4%)*

* Age groups were divided into quartiles
** Characteristic Pain Intensity (CPI)
*** Graded Chronic Pain Scale (GCPS)

Prevalence of referred pain at baseline and follow-up

Prevalence of referred pain among TMD cases is shown in Table 2 and Figure 1. Of the 614 TMD cases at baseline, 162 (26.4%) had a pain with referral, and 104 (36.4%) out of the 286 cases at follow-up had referred pain. Figures 2 and 3 shows the distribution of referred pain prevalence by the facial sites referring pain, with the highest being extraoral sites at both baseline and follow-up.

Table 2: Prevalence of referred pain at baseline and follow-up, and number of sites with referred pain among those with referred pain.

	Total sample N	***Referred pain n (%)***	***95%CI***	***Median***	***IQR****
Baseline	*614*	*162 (26.4%)*	(22.9 to 30.1)%	*2*	*1 to 4*
Follow-Up	*286*	*104 (36.4%)*	(30.7 to 42.2)%	*3*	*1 to 7*

* IQR = 25th to 75th percentile

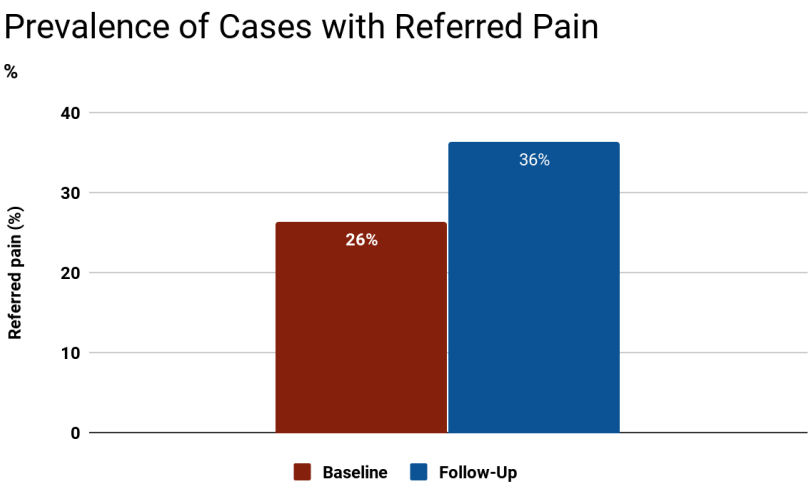

Figure 1: Prevalence of referred pain at baseline and follow-up

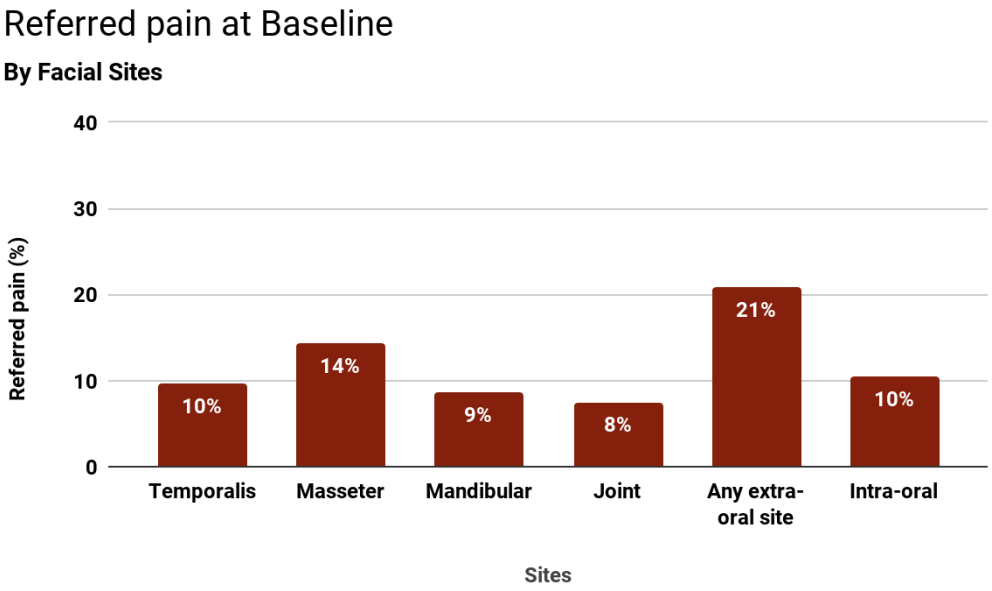

Figure 2: Prevalence of referred pain at baseline by facial site

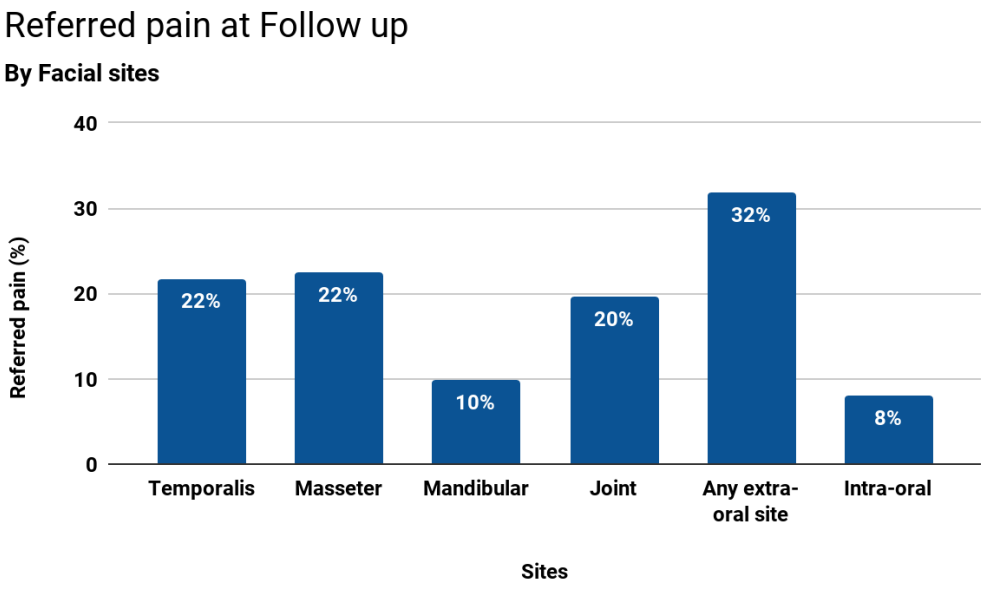

Figure 3: Prevalence of referred pain at follow-up by facial site

Risk factors for referred pain at baseline and follow-up

Females were more likely than males to have referred pain (27.9% vs. 16.7%; p-value = 0.025). The risk of having referred pain was not associated with age, race nor education (Table 3). Greater somatization, somatization without pain, as well as depression and anxiety, were all associated with an increased risk of referred pain (p-values <0.0001; Table 4). The number of bodily pain sites, GCPS, and CPI scores were significantly associated with a greater risk for having referred pain (p-values <0.001; Table 4). Having a TMD diagnosis of myofascial pain, arthralgia, or DJD were significant factors associated with referred pain (p-values <0.0001) likely because pain on palpation is a criterion for these diagnoses and subjects have to have pain on palpation to get the diagnosis of referred pain as well.

Table 3: Referred pain by subject demographics for TMD cases at baseline (n=614)

Demographic		*Total sample N (%)*	*Referred pain n (%)*	*P-value*
Gender	*Female*	*523 (85.2%)*	*146 (27.9%)*	*0.025*
	Male	*90 (14.7%)*	*15 (16.7%)*	
Age (years)*	*18 to 24*	*151 (24.6%)*	*40 (26.5%)*	*0.748*
	25 to 35	*155 (25.2%)*	*44 (28.4%)*	
	36 to 47	*145 (23.6%)*	*40 (27.6%)*	
	48 to 67	*163 (26.5%)*	*38 (23.3%)*	
Race	*American Indian/Alaskan Native*	*5 (0.8%)*	*2 (40.0%)*	*0.365*
	Asian	*21 (3.4%)*	*2 (9.5%)*	
	NonHispanic/Pacific Islander	*2 (0.3%)*	*0 (0.0%)*	
	Black/African American	*12 (2.0%)*	*3 (25.0%)*	
	White	*561 (91.4%)*	*150 (26.7%)*	
	>1 race	*12 (2.0%)*	*4 (33.3%)*	
Income (dollars)	*<10K*	*96 (15.6%)*	*27 (28.1%)*	*0.933*
	10-39K	*190 (30.9%)*	*48 (25.3%)*	
	40-79K	*196 (31.9%)*	*53 (27.0%)*	
	≥80K	*124 (20.2%)*	*31 (25.0%)*	
Education level	*Some college or less*	*274 (44.6%)*	*70 (25.5%)*	*0.571*

	College	*190 (30.9%)*	*55 (28.9%)*	
	Beyond college	*149 (24.3%)*	*36 (24.2%)*	

* Age groups were divided into quartiles

Table 4: Referred pain by self-report measures for TMD cases at baseline (n=614).

Self-report Measure		***Total sample at Baseline N (%)***	***Referred pain at Baseline n(%)***	***P-value***
Facial pain duration (years)	*>0 to <2*	*113 (18.4%)*	*30 (26.5%)*	*0.0738*
	2 to <6	*137 (22.3%)*	*39 (28.5%)*	
	6 to <13	*128 (20.8%)*	*38 (29.7%)*	
	13+	*131 (21.3%)*	*53 (40.5%)*	
Somatization	*Normal*	*172 (28.0%)*	*22 (12.8%)*	*< .0001*
	Moderate	*154 (25.1%)*	*36 (23.4%)*	
	Severe	*286 (46.6%)*	*103 (36.0%)*	
Somatization without pain items	*Normal*	*436 (71.0%)*	*93 (21.3%)*	*< .0001*
	Moderate	*107 (17.4%)*	*33 (30.8%)*	
	Severe	*69 (11.2%)*	*35 (50.7%)*	
Depression	*Normal*	*396 (64.5%)*	*90 (22.7%)*	*0.001*
	Moderate	*145 (23.6%)*	*40 (27.6%)*	
	Severe	*71 (11.6%)*	*31 (43.7%)*	
Anxiety	*Normal*	*491 (80.0%)*	*114 (23.2%)*	*0.001*
	Moderate	*80 (13.0%)*	*29 (36.3%)*	
	Severe	*40 (6.50%)*	*18 (45.0%)*	

Number of other pains	*0*	*88 (14.3%)*	*7 (8.0%)*	*< .0001*
	1	*168 (27.4%)*	*31 (18.5%)*	
	2	*211 (34.4%)*	*62 (29.4%)*	
	3	*106 (17.3%)*	*38 (35.8%)*	
	4	*39 (6.40%)*	*23 (59.0%)*	
CPI*	*0*	*112 (18.2%)*	*2 (1.8%)*	*< .0001*
	>0 to 40	*159 (25.9%)*	*34 (21.4%)*	
	>40 to 60	*188 (30.6%)*	*63 (33.5%)*	
	>60	*155 (25.2%)*	*63 (40.6%)*	
GCPS **	*0*	*112 (18.2%)*	*2 (1.8%)*	*< .0001*
	1	*215 (35.0%)*	*55 (25.6%)*	
	2a	*155 (25.2%)*	*50 (32.3%)*	
	2b	*66 (10.7%)*	*19 (28.8%)*	
	3 or 4	*62 (10.1%)*	*35 (56.5%)*	

* Characteristic Pain Intensity (CPI)
** Graded Chronic Pain Scale (GCPS)

Table 5: Referred pain by clinical diagnosis for TMD cases at baseline (n=614).

Baseline Clinical Diagnosis		*Total sample N(%)*	*Referred pain n(%)*	*P-value*
Myofascial pain	*No*	*119 (19.4%)*	*4 (3.4%)*	*< .0001*
	Yes	*495 (80.6%)*	*158 (31.9%)*	
Disk displacement	*No*	*101 (16.4%)*	*31 (30.7%)*	*0.282*
	Yes	*513 (83.6%)*	*131 (25.5%)*	
Arthralgia or DJD	*No*	*121 (19.7%)*	*9 (7.4%)*	*< .0001*
	Yes	*493 (80.3%)*	*153 (31.0%)*	

At follow-up, characteristics that were associated with referred pain were greater somatization, depression, GCPS, CPI scores, and number of other bodily pains, as well as having a TMD diagnosis of myofascial pain, arthralgia, or DJD (p-values <0.001). Results at follow-up are reported in Tables 6,7 and 8.

Table 6: Referred pain by subject demographics for TMD cases at follow-up (n=286).

Demographic		*Total sample N (%)*	*Referred pain n (%)*	*P-value*
Gender	*Female*	*255 (89.5%)*	*93 (36.5%)*	*0.842*
	Male	*30 (10.5%)*	*10 (33.3%)*	
Age(years)*	*18 to 24*	*76 (27.0%)*	*29 (38.2%)*	*0.363*
	25 to 35	*64 (22.7%)*	*24 (37.5%)*	
	36 to 47	*72 (25.5%)*	*20 (27.8%)*	
	48 to 67	*70 (24.8%)*	*29 (41.4%)*	
Race	*American Indian/Alaskan*	*2 (0.7%)*	*1 (50.0%)*	*0.684*

	Native			
	Asian	*6 (2.1%)*	*1 (16.7%)*	
	Non Hispanic/Pacific Islander	*1 (0.3%)*	*0 (0.0%)*	
	Black/African American	*5 (1.7%)*	*2 (40.0%)*	
	White	*265 (92.7%)*	*99 (37.4%)*	
	>1 race	*7 (2.4%)*	*1 (14.3%)*	
Income(dollars)	*<10K*	*18 (7.6%)*	*3 (16.7%)*	*0.258*
	10-39K	*42 (17.6%)*	*17 (40.5%)*	
	40-79K	*89 (37.4%)*	*31 (34.8%)*	
	≥80K	*89 (37.4%)*	*36 (40.4%)*	
Education level	*Some college or less*	*88 (31.0%)*	*34 (38.6%)*	*0.337*
	College	*126 (44.4%)*	*40 (31.7%)*	
	Beyond college	*70 (24.6%)*	*29 (41.4%)*	
Recruitment site	*UM*	*97 (33.9%)*	*33 (34.0%)*	*0.656*
	UW	*97 (33.9%)*	*34 (35.1%)*	
	UB	*92 (32.2%)*	*37 (40.2%)*	

* Age groups were divided into quartiles

Table 7: Referred pain by self-report measures for TMD cases at follow-up (n=286).

Self-report Measure		*Total sample N (%)*	*Referred pain n(%)*	*P-value*
Facial pain duration (years)	*>0 to <2*	*42 (23.1%)*	*16 (38.1%)*	*0.931*
	2 to <6	*39 (21.4%)*	*17 (43.6%)*	
	6 to <13	*52 (28.6%)*	*22 (42.3%)*	
	13+	*49 (26.9%)*	*22 (44.9%)*	
Somatization	*Normal*	*71 (24.9%)*	*19 (26.8%)*	*0.020*
	Moderate	*88 (30.9%)*	*28 (31.8%)*	
	Severe	*126 (44.2%)*	*57 (45.2%)*	
Somatization without pain items	*Normal*	*183 (64.2%)*	*63 (34.4%)*	*0.244*
	Moderate	*63 (22.1%)*	*22 (34.9%)*	
	Severe	*39 (13.7%)*	*19 (48.7%)*	
Depression	*Normal*	*178 (62.5%)*	*50 (28.1%)*	*0.0002*
	Moderate	*60 (21.1%)*	*34 (56.7%)*	
	Severe	*47 (16.5%)*	*20 (42.6%)*	
Number of other pains (headache, chest, back or stomach)	*0*	*29 (10.2%)*	*6 (20.7%)*	*< 0.0001*
	1	*72 (25.3%)*	*13 (18.1%)*	
	2	*110 (38.6%)*	*46 (41.8%)*	
	3	*66 (23.2%)*	*34 (51.5%)*	
	4	*8 (2.8%)*	*5 (62.5%)*	
CPI*	*0*	*37 (13.0%)*	*0 (0.0%)*	*< 0.0001*

	>0 to 40	*78 (27.4%)*	*22 (28.2%)*	
	>40 to 60	*108 (37.9%)*	*52 (48.1%)*	
	>60	*62 (21.8%)*	*30 (48.4%)*	
GCPS	*0*	*37 (13.0%)*	*0 (0.0%)*	*< 0.0001*
	1	*198 (69.7%)*	*80 (40.4%)*	
	2a	*27 (9.5%)*	*15 (55.6%)*	
	2b	*2 (0.7%)*	*0 (0.0%)*	
	3 or 4	*20 (7.0%)*	*9 (45.0%)*	

* Characteristic Pain Intensity,
** Graded Chronic Pain Scale

Table 8: Descriptives and tests for referred pain for TMD cases at follow-Up (n=286).

Clinical Diagnosis		***Total sample N(%)***	***Referred pain n(%)***	***P-value***
Myofascial pain	*No*	*76 (26.8%)*	*74 (97.4%)*	*< 0.0001*
	Yes	*208 (73.2%)*	*101 (48.6%)*	
Disk displacement	*No*	*100 (35.2%)*	*57 (57.0%)*	*0.095*
	Yes	*184 (64.8%*	*60 (32.6%*	
Arthralgia or DJD	*No*	*67 (23.6%*	*61 (91.0%*	*< 0.0001*
	Yes	*217 (76.4%*	*97 (44.7%*	

Persistence of referred pain from baseline to follow-up

Over half (57.4%) of the baseline subjects who were diagnosed with myofascial pain with referral at baseline continued having the condition at follow-up (Table 9). The highest rate of persistence among facial sites was for temporalis muscles and TMJ sites (Figure 4).

Table 9: Rate of referred pain at follow-up by referred pain at baseline

Referred pain at baseline	*Total N%*	*Referred pain at Follow up n(%)*	95%CI
No(New RP)	*243 (72.1%)*	*48 (19.8%)*	14.9 to 25.3%
Yes(Persistence)	*94 (27.9%)*	*54 (57.4%)*	46.8 to 67.6%

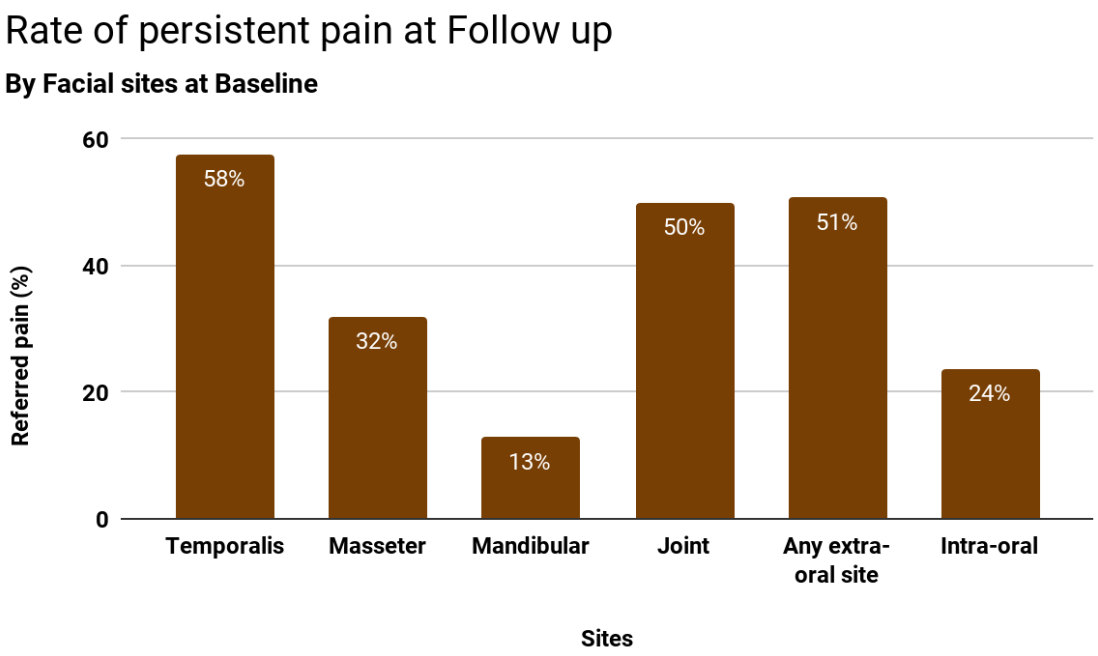

Figure 4: Rate of persistent referred pain by facial site

Predictors of persistence of referred pain from baseline to follow-up

Characteristic pain intensity (CPI) score at baseline was the only factor significantly associated with persistence of referred pain (p = 0.02; Table 11). Results of assessing the relationship of baseline factors with persistence of referred pain at follow-up are reported in Tables 10,11 and 12.

Table 10: Persistence of referred pain at follow-up by subject demographics (n=94) *

Demographic		*Total sample N (%)*	*Persistent referred pain** n (%)*	*P-value*
Gender	*Female*	*86 (92.5%)*	*48 (55.8%)*	*0.695*
	Male	*7 (7.5%)*	*5 (71.4%)*	
Age(years)***	*18 to 24*	*22 (23.4%)*	*13 (59.1%)*	*0.090*
	25 to 35	*21 (22.3%)*	*13 (61.9%)*	
	36 to 47	*28 (29.8%)*	*11 (39.3%)*	
	48 to 67	*23 (23.4%)*	*17 (73.9%)*	
Race	*American Indian/Alaskan Native*	*1 (1.1%)*	*0 (00.0%)*	*0.315*
	Asian	*1 (1.1%)*	*1 (100%)*	
	NonHispanic/Pacific Islander	*1 (1.1%)*	*1 (100%)*	
	Black/African American	*88 (93.6%)*	*52 (59.1%)*	
	White	*3 (3.2%)*	*0 (0.0%)*	
	>1 race	*1 (1.1%)*	*0 (0.0%)*	
Income(Dollars)	*<10K*	*13 (14.1%)*	*7 (53.8%)*	*0.961*
	10-39K	*26 (28.3%)*	*14 (53.8%)*	
	40-79K	*37 (40.2%)*	*21 (56.8%)*	
	≥80K	*16 (17.4%)*	*10 (62.5%)*	
Education level	*Some college or less*	*37 (39.8%)*	*20 (54.1%)*	*0.897*

	College	*31 (33.3%)*	*18 (58.1%)*	
	Beyond college	*25 (26.9%)*	*15 (60.0%)*	
Recruitmint site	*UM*	*31 (33.0%)*	*16 (51.6%)*	*0.495*
	UW	*41 (43.6%)*	*23 (56.1%)*	
	UB	*22 (23.4%)*	*15 (68.2%)*	

*162 TMD cases with referred pain in the baseline study, and 94 of the 162 were followed in the follow-up study
**Persistent referred pain: Referred pain at follow-up among subjects with referred pain at baseline.
*** Age groups were divided into quartiles

Table 11: Persistent referred pain at follow-up by self-report measures (n=94)*.

Self-report measure		***Total sample N (%)***	***Persistent referred pain** n(%)***	***P-value***
Facial pain duration (years)	*>0 to <2*	*14 (14.9%)*	*8 (57.1%)*	*0.726*
	2 to <6	*24 (25.5%)*	*16 (66.7%)*	
	6 to <13	*22 (23.4%)*	*11 (50.0%)*	
	13+	*34 (36.2%)*	*19 (55.9%)*	
Somatization	*Normal*	*12 (12.9%)*	*4 (33.3%)*	*0.215*
	Moderate	*24 (25.8%)*	*15 (62.5%)*	
	Severe	*57 (61.3%)*	*34 (59.6%)*	
Somatization without pain items	*Normal*	*54 (58.1%)*	*29 (53.7%)*	*0.738*
	Moderate	*16 (17.2%)*	*10 (62.5%)*	
	Severe	*23 (24.7%)*	*14 (60.9%)*	
Depression	*Normal*	*50 (53.8%)*	*25 (50.0%)*	*0.230*

	Moderate	*24 (25.8%)*	*17 (70.8%)*	
	Severe	*19 (20.4%)*	*11 (57.9%)*	
Anxiety	*Normal*	*59 (63.4%)*	*33 (55.9%)*	*0.907*
	Moderate	*23 (24.7%)*	*13 (56.5%)*	
	Severe	*11 (11.8%)*	*7 (63.6%)*	
Number of other pains	*0*	*4 (4.3%)*	*1 (25.0%)*	*0.224*
	1	*19 (20.4%)*	*8 (42.1%)*	
	2	*36 (38.7%)*	*25 (69.4%)*	
	3	*19 (20.4%)*	*11 (57.9%)*	
	4	*15 (16.1%)*	*8 (53.3%)*	
CPI*	*0*	*1 (1.10%)*	*0 (0.0%)*	*0.025*
	>0 to 40	*17 (18.1%)*	*5 (29.4%)*	
	>40 to 60	*38 (40.4%)*	*24 (63.2%)*	
	>60	*38 (40.4%)*	*25 (65.8%)*	
GCPS**	*0*	*1 (50.0%)*	*0 (0.0%)*	*0.171*
	1	*30 (54.5%)*	*13 (43.3%)*	
	2a	*31 (62.0%)*	*22 (71.0%)*	
	2b	*14 (73.7%)*	*8 (57.1%)*	
	3 or 4	*17 (48.6%)*	*10 (58.8%)*	

*162 TMD cases with referred pain in the baseline study, and 94 of the 162 were followed in the follow-up study

**Persistent referred pain: Referred pain at follow-up among subjects with referred pain at baseline.

*** Characteristic Pain Intensity, ****Graded Chronic Pain Scale

Table 12: Persistence of referred pain at follow-up by clinical diagnosis (n=94)*

Clinical diagnosis		*Total sample N(%)*	*Persistent referred pain* n (%)*	*P-value*
Myofascial pain	*No*	*91 (96.8%)*	*53 (58.2%)*	*0.573*
	Yes	*1 (1.50%)*	*2 (66.7%)*	
Disk displacement	*No*	*77 (58.8%)*	*42 (54.5%)*	*0.284*
	Yes	*14 (45.2%)*	*5(29.4%)*	
Arthralgia or DJD	*No*	*89 (94.7%)*	*51 (57.3%)*	*1.00*
	Yes	*4 (5.90%)*	*2 (40.0%)*	

*162 TMD cases with referred pain in the baseline study, and 94 of the 162 were followed in the follow-up study
**Persistent referred pain: Referred pain at follow-up among subjects with referred pain at baseline

Impact of referred pain on TMD prognosis

Prognosis for TMD diagnoses at follow-up by referred pain at baseline

After adjusting for variables of interest at baseline, having referred pain at baseline was associated with higher odds of having a diagnosis of myofascial pain at follow-up (OR = 2.61; 95% CI, 1.37 to 4.94), disk displacement (OR = 1.88; 95% CI, 1.13 to 3.11) and arthralgia or DJD (OR = 3.45; 95% CI, 1.84 to 6.46) (Table 13). There was no evidence of an interaction effect between referred pain and the diagnosis at baseline on the odds having the diagnosis at follow-up (all p-values >0.05). The overall number of cases for each diagnosis at baseline and follow-up is shown in Table 18 in the appendix.

Table 13: Logistic regression results for TMD diagnoses at follow-up

Outcome	*Predictor variable*	*Odds Ratio (95%CI)*	*P-value*
Myofascial pain at Follow-Up	*Diagnosis at Baseline (Yes vs. No)*	*16.65 (7.78, 35.63)*	*< .0001*
	Referred pain at Baseline (Yes vs. No)	*2.61 (1.37, 4.94)*	*.0033*
Disc Displacement at Follow-Up	*Diagnosis at Baseline (Yes vs. No)*	*3.38 (1.83, 6.21)*	*< .0001*
	Referred pain at Baseline (Yes vs. No)	*1.88 (1.13, 3.11)*	*.0145*
Arthralgia or DJD at Follow-Up	*Diagnosis at Baseline (Yes vs. No)*	*4.88 (2.65, 8.95)*	*< .0001*
	Referred pain at Baseline (Yes vs. No)	*3.45 (1.84, 6.46)*	*.0001*

Prognosis for characteristic pain intensity (CPI) at follow-up by referred pain at baseline

After adjusting for characteristic pain intensity (CPI) at baseline, subjects with any referred pain at baseline had on average a higher CPI at follow-up by 4.6 points (95% CI, -0.1 to 9.3; p-value 0.056). There was no evidence of an interaction effect between referred pain and CPI at baseline (p-value = 0.15), Table 14.

Table 14: Linear regression results for characteristic pain intensity (CPI) at follow-up.

	Coefficient estimate (95% CI)	*P-value*
Referred pain at baseline (yes vs. no)	*4.6 (-0.1 to 9.3)*	*0.056*
CPI at baseline	*0.36 (0.28, 0.44*	*<0.0001*

Prognosis for graded chronic pain score (GCPS) at follow-up by referred pain at baseline

Using a multinomial logistic regression analysis and after adjusting for GCPS at baseline, there was not a significant association between referred pain at baseline and GCPS at follow-up (p-value = 0.24). However, the odds of having a GCPS of 3 or 4 (versus 0) were marginally significantly higher for subjects with referred pain at baseline (OR = 3.36; 95% CI 0.96 to 11.71; p-value = 0.057) (Table 15). Due to the small sample size, it was not possible to assess for an interaction effect between referred pain and GCPS at baseline (i.e., the model that included an interaction effect did not converge).

Table 15: Multinomial logistic regression results for graded chronic pain scale (GCPS) at follow-up

	GCPS	***Odds Ratio (95% CI)***	***P-value***
Referred pain at Baseline (yes vs. no)	*Score of 1 (vs. 0)*	*1.85 (0.78, 04.37)*	*.16*
	Score of 2 (vs. 0)	*1.35 (0.42, 04.33)*	*.61*
	Score of 3 or 4 (vs. 0)	*3.36 (0.96, 11.71)*	*.057*
			Overall p-value
			.24

Prognosis for somatization at follow-up by referred pain at baseline

After adjusting for somatization at baseline, referred pain at baseline was not significantly associated with somatization at follow-up (p-value = 0.84). For example, the odds ratio of having severe somatization (versus normal) was 1.11 for subjects with referred pain at baseline compared to those without referred pain (95% CI 0.57 to 2.14; p-value = 0.75). Similarly, after adjusting for somatization without pain at baseline, referred pain at baseline was not significantly associated with somatization without pain at follow-up (p-value = 0.50). Due to the small sample size, it was not possible to assess for an interaction effect between referred pain and somatization or somatization without pain at baseline.

Prognosis for depression at follow-up by referred pain at baseline

After adjusting for depression at baseline, referred pain at baseline was significantly associated with moderate depression at follow-up (p-value = .028). Subjects with referred pain at baseline had higher odds of having moderate depression versus no (normal) depression at follow-up (OR = 1.97; 95% CI, 1.07 to 3.59). However, the odds of having severe depression (versus no depression) was not higher (OR = 0.62; 95% CI, 0.238 to 1.37) (Table 16). Due to small sample size, it was not possible to assess for an interaction effect between referred pain and depression at baseline.

Table 16: Multinomial logistic regression results for depression at follow-up*

	Depression at follow-up	***Odds Ratio (95% CI)***	***P-value***
Referred pain at Baseline (yes vs. no)	*Moderate (vs. Normal)*	*1.97 (1.07, 3.59)*	*.028*
	Severe (vs. Normal)	*0.62 (0.28, 1.37)*	*.24*
			Overall p-value
			.014

*Depression at baseline is adjusted for in the multinomial logistic regression (results not shown)

Prognosis for the number of other pain conditions at follow-up by referred pain at baseline

After adjusting for the number of other pain conditions at baseline, referred pain at baseline was not significantly associated with the number of other pain conditions at follow-up (OR = 1.20; 95% CI, 0.75 to 1.89; p-value = 0.44). However, there was evidence of an interaction between the number of other pain conditions and referred pain at baseline (p-value = 0.038). Subjects with referred pain at baseline had higher odds of having a greater number of other pain conditions at follow-up (OR = 1.69; 95% CI, 1.05 to 2.72) (Table 17).

Table 17: Ordinal logistic regression results for number of other pain conditions at follow-up by number of other pain conditions and referred pain at baseline.*

	Number of Other Pain Conditions at Baseline	*Odds Ratio (95% CI)*	*P-value*
Referred pain at Baseline (yes vs. no)	*0 pain conditions*	*1.69 (1.05, 2.72)*	*.029*
	1 pain conditions	*1.36 (0.99, 1.86)*	*.051*
	2 pain conditions	*1.10 (0.87, 1.38)*	*.43*
	3 pain conditions	*0.88 (0.65, 1.20)*	*.42*
	4 pain conditions	*0.71 (0.44, 1.13)*	*.15*

*There was an interaction effect between referred pain and number of other pain conditions at baseline for the odds of referred pain at follow-up (p-value = 0.038). Therefore, odds ratios for referred pain at baseline (yes vs. no) are reported by the number of other pain conditions at baseline.

Discussion

Our definition of referred pain adheres to the validated definition of myofascial pain with referral in the DC/TMD. The prevalence of referred pain in Temporomandibular Disorder (TMD) cases in our study was around 30%. At baseline, 26.4% of cases had at least one referred pain site. A similar but slightly higher rate of cases with referred pain was present at follow-up where 36.4% of TMD cases had at least one referred pain site. Extraoral sites that include the largest masticatory muscle groups (temporalis and masseter muscles) as well as TMJ poles, had the highest prevalence of the presence of referred pain among all muscles and structures examined. The rate of persistence of referred pain from baseline to follow-up in TMD cases was 57.4%. The temporalis muscle had the highest rate of persistence of referred pain over a period of 8 years.

Among the demographics we assessed, female gender was the only risk factor associated with the presence of referred pain, and only at baseline. The overall prevalence of TMD is known to be higher among females than males (Drangsholt and LeResche 1999) and as mentioned earlier, females had the highest prevalence of referred pain after experimental injection (Schmidt-Hansen et al. 2007) and an overall higher pain intensity and a greater pain area after experimental injection of masseter muscle (Cairns et al. 2001). The significant association of referred pain with SCL-90R psychosocial factors in our analysis supports the hypothesis of the association of referred pain with

central sensitization. Somatization was associated with the presence of referred pain at baseline and follow-up. On the other hand, somatization without pain items was a significant factor only at baseline. Depression was associated with the presence of referred pain at both baseline and follow-up. Anxiety, which was only measured at baseline, was also significantly associated with referred pain. At both baseline and follow-up, the number of other pain conditions, CPI and GCPS were all associated with the presence of referred pain.

To relate an explanatory model for referred pain physiologically, in general, pain may include the following physiologic responses: autonomic, inflammatory, emotional and nociceptive changes (Okeson 2005). Autonomic and inflammatory changes may account for different bodily symptoms such as hypertension, increased heart rate, hyperventilation, sweating, acid reflux, dizziness and many other symptoms (Sessle 2000). These symptoms relate strongly to the presence of somatic symptoms that cannot be explained by the presence of any tissue damage (Dworkin 1994, Rief and Broadbent 2007). Emotional changes may include anxiety and/or depression as well as other behavioral and cognitive changes that can impact disability (Dworkin 1994).

When it comes to TMD diagnostic categories, it makes perfect sense that referred pain would be associated with diagnoses involving pain (myofascial pain and arthralgia). In our analysis having a myofascial pain, arthralgia or DJD diagnosis was significantly associated with referred pain at baseline and follow-up.

Our results are parallel with the widely accepted and supported idiopathic pain model, and the results support most of the data and clinical studies on chronic pain and their associated psychosocial factors (Diatchenko et al. 2006). These results also emphasize the importance of assessing and managing psychosocial factors in patients with chronic musculoskeletal pain (Palla 2011). This model of pain has been conceptualized for orofacial pain conditions, specifically TMD (Ohrbach 2003). Based on our results, referred pain at baseline turned out to be an independent predictor for higher CPI scores at follow-up; therefore, it is important to carefully assess all domains in patients with referred pain. Characteristic pain intensity was the only factor at baseline that predicted the persistence of referred pain. Thus, CPI is a more important predictor of the persistence of referred pain than are baseline psychosocial factors. CPI is a measure of subjective pain intensity. The discrimination of intensity depends on the two domains: 1) The sensory-discriminative part, which allows localization and discrimination of quality and may be modified biologically by different chemical

mediators of inflammation and autonomic response (Merskey and Bogduk 1994, Sessle 2000); and 2) The motivational-affective component of pain that allows the discrimination of intensity and may be modified by emotions, cognitive behavioral factors and prior experience (Merskey and Bogduk 1994, Sharav and Benoliel 2008). These concepts of intensity discrimination conclude that a painful stimulus can produce many overlapping changes on both the sensory and emotional affective levels, while other authors might argue that intensity is exclusively a sensory-discriminative domain. It is useful however to recall the official definition of pain by the International Association for the Study of Pain, "pain" is defined as an unpleasant sensory and emotional experience that occurs in the presence of tissue damage or is described in terms of such damage (Merskey and Bogduk 1994). The definition clearly indicates that pain is a biopsychosocial dysfunction complex and not only a sensory phenomenon (Palla 2011).

Looking at the impact that referred pain has on the prognosis of TMD over an 8 year period, the odds were higher for several outcomes at follow-up. The probability of a myofascial pain diagnosis or a diagnosis of arthralgia at follow-up was significantly elevated among those with referred pain at baseline. after controlling for baseline diagnosis, TMD cases with referred pain also had marginally significant higher odds of having a grade 3 or 4 on the GCPS scale at follow-up. Odds were also increased for having moderate depression at follow-up for cases having referred pain at baseline. Our results were consistent with those shown in the OPPERRA study (Maixner et al. 2011) where depression has been implicated as a potential risk factor for the development of painful TMD. In addition, several studies have reported that patients with TMD express high levels of depression and other multiple psychological factors (Vassend et al. 1995, Slade et al. 2007).

Improved understanding of the factors associated with presence and persistence of referred pain in persons with a regional pain condition, in this case, TMD, is clinically relevant for understanding the impact and severity of such conditions on affected individuals. Understanding the mechanisms associated with referred pain and whether a referral is purely peripheral versus central helps to provide insight into the management of patients and particularly those whose focus is pain in the referred pain site. If the process of referred pain is peripheral, then local treatment approaches may be more applicable. However, if it is central, then behavioral or centrally targeted pharmacological approaches may be more appropriate.

The finding of referred pain from the TMJ palpation protocol tends to refute the hypothesis that referred pain trigger points come only from muscular tissues or specific physical structures, i.e.; “taut bands” that are commonly known to be associated with localized and referred pain. This finding strengthens the concept of referred pain being more associated with central neuroplastic changes (Sessle 1990, Sessle 2000).

Referred pain can be identified without characterizing a taut band. The literature indicates that referred pain is an important phenomenon that characterizes a trigger point (TrP). A TrP is usually encountered within a physical taut band that is in turn necessary to diagnose Myofascial Pain Syndrome (MPS). In data we used from the RDC/TMD validation study, the methodology to identify referred pain (Myofascial pain with referral) in the craniofacial region was based on palpation of the designated RDC/TMD sites and did not include the identification of a taut band. Another part of the validation study attempted to follow the exact methodology to identify taut bands according to the diagnostic criteria for myofascial pain syndrome (Travell and Simons 1983, Fricton et al. 1985, Fricton and Schiffman 1986, Fricton 1993, Simons 1996). But, in order to ensure that the same definition of referred pain was used at baseline and follow-up, we did not analyze those data. It is important to point out that identifying trigger points does not necessarily correspond to a tangible taut band (Ohrbach and Gale 1989) and that pain at a distant site can be triggered by experimental injections (Svensson et al. 2003). Referred pain is only one of the signs of an active trigger point, other validated reliable signs include the local twitch response and local tenderness in addition to pain referral (Gerwin et al. 1997).

In the literature, it is clear that referred pain patterns occur under special central sensitization and neuroplasticity alterations. For this phenomenon to occur, certain sensory-discriminative, as well as emotional-affective changes, are required. Other than autonomic, inflammatory and emotional changes, nociceptive changes also take place (Okeson 2005). Nociceptive changes can occur peripherally as well as centrally at the second order neuron at the level of spinothalamic ganglion located at the subnucleus caudalis of the brain stem (Hu and Sessle 1988). At this level, afferent inputs from the trigeminal ganglion may undergo convergence through either nociceptive specific neurons (NS) that transmit pain or through wide dynamic range (WDR) neurons that may transmit a wider range of sensations including painful stimuli (Hu and Sessle 1988, Sessle 2000). These changes, along with deficits in descending pain modulation, are thought to produce a variety of

abnormal responses including dynamic tactile allodynia, pressure hyperalgesia, enhanced temporal summation, lower pain threshold and referred pain (Hu and Sessle 1988, Sessle 2000). The activation of the WDR neurons follows the neuromatrix theory or the gate control theory of pain by Melzack (Melzack and Wall 1965) Due to these secondary neurosensory changes, central sensitization occurs at higher thalamic levels (3rd order neurons), which provokes more changes on the emotional and physiological levels (Dworkin 1994). Glial cell activation and immune responses act as an allostatic response in an attempt to normalize the physiologic changes that have occurred (McEwen 1998). An allostatic response is the body's natural way to produce homeostasis, however, these changes are also known as factors that play a role in migraines, irritable bowel syndrome and gastroesophageal reflux syndromes (Yamamura et al. 1999, Van Handel and Fass 2005, Price et al. 2006). At this level, emotional distress arising from the limbic system could include suffering, disability, guarded musculoskeletal behavior, as well as enhancing negative cognitive thoughts such as catastrophizing and pain taking over daily life (Turner and Aaron 2001, Sharav and Benoliel 2008). Once this chronicity level is achieved, neuroplasticity or neuro-plastic alterations occur and the up-down regulation of a nociceptive behavior resumes and probably persists in the absence of proper intervention and assessment (Sharav and Benoliel 2008).

Strengths and Limitations

Our analysis was the first to look at referred pain and its persistence in TMD cases and to analyze associated factors and possible outcomes over a period of 8 years.

However, the Validation study was not directly designed to define and characterize referred pain, therefore there are several study limitations. First, although definitions and characterization of trigger points and taut bands have well-established reliability for a number of skeletal muscles, the validation study examination did not take the characterization of trigger points and taut bands into account. Second, the reference zones to which the pain was referred were not recorded, nor reported in terms of familiarity. Recording reference zones would have been ideal to match the methodology of referred pain clinical studies. Third, by design, baseline and follow-up studies did not use random sampling; not all TMD diagnostic groups were randomly included and therefore sample sizes do not mirror the distribution of diagnostic groups in the TMD population. Finally, the small number of

controls in the baseline study limited the analysis of predictors of onset of TMD and referred pain at follow-up.

Conclusion

Our results indicate that referred pain may occur upon palpation of sites other than a traditionally defined trigger point. Our results, however, do not contradict the research and studies that focus on physically localizing the peripheral phenomenon of trigger points and their associated physiological and physical signs and symptoms. In the orofacial region, based on our findings, identifying referred pain in masticatory muscles diagnosed with myalgia does not require specific identification of a fibrous structured taut band. The validated, reliable operational definitions of the DC/TMD are enough to identify and diagnose referred pain.

Referred pain is best characterized as part of the central sensitization mechanism of pain and therefore may indicate its association with several factors that are directly related to central phenomena. Referred pain correlates positively with the severity index of pain since it is related to the increase in characteristic pain intensity (CPI). Referred pain may also impact depression, somatization, and number other bodily pains as well as disability days. Referred pain may be an indication of increased pain severity and suffering.

Referred pain is an important marker for assessment and management of any orofacial pain condition. In addition to indicating an increased central sensitivity, it may also reveal the true pain source in a pain condition that has otherwise been misdiagnosed.

Table 18: Referred pain by TMD diagnosis from baseline to follow-up

Baseline	*Referred Pain at Baseline*	*Follow-up N*	*Referred pain at follow-up n(%)*
Myofascial pain			
No	*No*	*72*	*9 (12.5%)*
	Yes	*3*	*0 (0%)*
Yes	*No*	*171*	*116 (67.8%)*
	Yes	*91*	*78 (85.7%)*
Disk displacement			
No	*No*	*43*	*12 (27.9%)*
	Yes	*17*	*6 (35.3%)*
Yes	*No*	*200*	*108 (54.0%)*
	Yes	*77*	*54 (70.1%)*
Arthralgia and DJD			
No	*No*	*62*	*15 (24.2%)*
	Yes	*5*	*4 (80.0%)*
Yes	*No*	*181*	*116 (64.1%)*
	Yes	*89*	*75 (84.3%)*

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