A CLINICAL STUDY ON THE EFFECTS OF TREATING TEMPOROMANDIBULAR DISORDER (TMD) BY LOW LEVEL LASER THERAPY (LLLT), CONSERVATIVE AND COMBINATION TREATMENTS

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by

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LIST OF ABBREVIATION

TMJ	Temporomandibular joint
TMD	Temporomandibular joint disorder
LLLT	Low level laser thyrapy
VAS	Visual analouge scale
ANOVA	Analysis of varaiance
Hs-CRP	High sensitive C reractive protein
IL-1	Interleukine 1
IL-6	Interleukine 6
IL-8	Interleukine 8
NSPSE	Nonspescific physical symtooms excluding pain
NSPSI	Nonspescific physical symtooms including pain
USM	Universiti Sains Malyasia
VRS	Verbal rating scale
NRS	Numerical rating sclae
SF-MPQ	McGill Pain Questionnaire short form
BPI-SF	Brief pain inventory short form
PSPI	Psychosocial pain index
MMPI	Minnesota multiphasic personality inventory
BAI	Beck Anxiet inventory
AAOP	American Academy of Orofacial Pain
CMI	Craniomandibular index
ICHD-II	International Classification of Headach and Diseaeses, 2nd edition
HIS	International Headache Society
AACD	American Academy of Craniomandibular Disorders
RDC/TMD	Research Diagnostic Criteria for TMD
Mal-RDC/TMD	Malay language /Research Diagnostic Criteria for TMD
CT	Coputed tomography
MRI	Magnatic resonance imaging
NSAID	Non steriodal anti-inflamatory drugs
TENS	Transcutaneous electrical nerve stimulation
SM	Self management
Nd: YAG	Neodymium:Yttrium aluminium garnet
Er: YAG	Erbium : Yttrium aluminium garnet
FDA	Food and drug adminstration
Er , Cr:YSGG	Erbium, chromium yttrium scandium-gallium-garnet
EMG	Electromyographic activity
MAVO	Maximum active vertical opening
MPVO	Maximum passive vertical opening
NIH	National institute of health
NINDS	National institute of neurological disorders and stroke
QoL	Quality of life
COMT	Catechol-O-methyltransferase
QST	Quantitative sensory testing

KAJIAN KLINIKAL KESAN MERAWAT GANGGUAN TEMPOROMANDIBULAR (TMD) OLEH TERAPI LASER PERINGKAT RENDAH (LLLT), RAWATAN KONSERVATIF DAN RAWATAN GABUNGAN.

ABSTRAK

Gangguan temporomandibular (TMD) ialah istilah biasa untuk sekumpulan penyakit muskuloskeletal yang dikaitkan dengan kesakitan dan/atau kerosakan pada otot mengunyah. Ia lazim dalam kalangan orang Asia dan Malaysia. Modaliti rawatan yang melibatkan conservative dan LLLT belum disiasat secara meluas, walaupun potensinya wujud. Matlamat kajian ini ialah untuk membandingkan kesan rawatan TMD dengan terapi laser tahap rendah (LLLT), rawatan konservatif standard (terapi berasaskan rumah) dan rawatan gabungan. Sejumlah 32 pesakit yang berumur 18 tahun ke atas telah didaftarkan dalam tiga kumpulan berbeza: 10 (konservatif), 11 (LLLT), dan 11 (gabungan). Kaedah persampelan bertujuan telah digunakan. Proforma sejarah dan pemeriksaan pesakit dan soal selidik terjemahan Mal-RDC/TMD yang disahkan telah digunakan. Kesakitan diukur dengan Skor Analog Visual (VAS). Pesakit dalam kumpulan LLLT sahaja dan kumpulan rawatan gabungan telah dirawat dengan 5 sesi laser tahap rendah setiap hari selama 10 hari. Pesakit dalam kumpulan rawatan konservatif dan kumpulan rawatan gabungan menerima rawatan TMD konservatif standard (kaunseling diet dan tekanan emosi, senaman rahang, terapi fizikal). Sampel darah telah dikumpulkan dari semua kumpulan dengan menggunakan langkah berjaga-jaga sejagat untuk venipuncture bagi membandingkan hs-CRP, IL-6, IL-8. Analisis deskriptif dan ukuran berulang ANOVA digunakan untuk analisis data. Di antara tiga

kumpulan (LLLT, konservatif, dan rawatan gabungan), terdapat perbezaan yang signifikan secara statistik dalam purata IL-6 ($p = 0.037$) dan IL-8 ($p = 0.001$). Perbandingan dari peringkat awal dengan selepas rawatan, didapati tahap kebimbangan di kalangan pesakit menurun secara mendadak, walaupun kumpulan itu tidak berbeza dengan ketara. Perbandingan dari garis dasar dengan selepas rawatan, purata skor indeks kemurungan menurun selepas rawatan. Tiada perbezaan yang ketara antara kedua-dua kumpulan dari segi kerosakan rahang selepas terapi ($p < 0.001$). Skor intensiti kesakitan kronik, skor NSPE ($p = 0.009$) dan NSPSI ($p < 0.001$) berkurangan dengan ketara dari garis dasar berbanding dengan pasca rawatan, tetapi tidak signifikan antara kumpulan. Purata pergerakan sisi juga ada perbezaan yang ketara ($p < 0.001$). Pembukaan mulut maksima dibantu dan tanpa bantuan menunjukkan perbezaan yang ketara ($p < 0.001$). Purata VAS menurun dengan ketara ($p < 0.001$) dari garis dasar kepada 12 minggu dan antara tiga kumpulan ($p < 0.010$). Perubahan ketara telah diperhatikan dalam IL-6 dan IL-8. Antara tiga kumpulan rawatan, LLLT dan pendekatan rawatan gabungan (LLLT + konservatif) didapati lebih baik daripada rawatan konservatif sahaja.

A CLINICAL STUDY ON THE EFFECTS OF TREATING TEMPOROMANDIBULAR DISORDER (TMD) BY LOW LEVEL LASER THERAPY (LLLT), CONSERVATIVE AND COMBINATION TREATMENTS.

ABSTRACT

Temporomandibular disorders (TMD) are a common term for a group of musculoskeletal diseases that are associated with pain and/or malfunction in the chewing muscles. They are prevalent among Asians and Malaysians. Treatment modalities involving conservative and LLLT have not been widely investigated, although their potential exists. The aim of this study was to compare the effects of treating TMD by low level laser therapy (LLLT), standard conservative treatment (home based therapy) and the combination treatments. A total of 32 patients aged 18 years and above with TMD were enrolled in three different groups:10 (conservative), 11 (LLLT), and 11 (combined treatments). Purposive sampling method was applied. A proforma for the patient's history and examination and validated translated questionnaires of Mal-RDC/TMD were used. Pain was measured by Visual Analogue Score (VAS). Patients in LLLT only group and combined treatment group were treated with 5 sessions of low-level laser every other day for a duration of 10 days. Patients in conservative treatment group and combined treatment group received standard conservative TMD treatment (diet and stress counseling, jaw exercises, physical therapy). Blood samples were collected from all groups following universal precautions for venipunctures in comparing hs-CRP, IL-6, IL-8. Descriptive analysis and Repeated measures ANOVA were used for data analysis. Between the three

groups (LLLT, conservative, and combined treatment), there was a statistically significant difference in the mean levels of IL-6 ($p = 0.037$) and IL-8 ($p = 0.001$). From baseline to post-treatment, the level of anxiety amongst the patients dramatically lowered, although the group did not differ significantly. From baseline to post-treatment, the mean depression index score decreased because of the treatment. There was no significant difference between all treatment groups in terms of jaw disabilites following therapy ($p =0.244$). Chronic pain intensity score, NSPSE ($p = 0.009$) score and NSPSI ($p < 0.001$) significantly decreased from baseline to post treatment, but not significant between the groups. Mean lateral excursion, maximum assisted and unassisted mouth opening all showed significant difference ($p < 0.001$) before and after the treatment. The mean of VAS significantly ($p < 0.001$) decreased from baseline to 12 weeks and between three groups ($p < 0.010$). A significant change was noticed in IL-6 and IL-8. Among the groups with three different treatment modalities, LLLT and combination (LLLT + conservative) treatment approaches were found to be better than the conservative treatment alone.

CHAPTER ONE

INTRODUCTION

1.1 Temporomandibular joint disorder

Temporomandibular disorders (TMD) are a common term for a group of musculoskeletal diseases that are associated with pain and/or malfunction in the chewing muscles, temporomandibular joints (TMJ), and components related to them (Kapos *et al*., 2020). It is the most common source of non-odontogenic orofacial pain and can be found in patients presenting with facial/head pain, TMJ and/or teeth, jaw function limitations, and sounds during jaw movements in the TMJ (Gil-Martínez *et al*., 2018; Kapos *et al*., 2020; Zakrzewska *et al.,* 2015). A variety of other symptoms may occur, such as tinnitus, abnormal swallowing, and hyoid bone tenderness (Demirkol *et al*., 2017). These TMD symptoms compromise quality of life (QoL) (Bitiniene *et al*., 2018), sleep, and psychological well-being, leading to anxiety, stress, depression, and a negative effect on social function, emotional health, and energy level (Durham *et al*., 2015b; Oliveira *et al*., 2015; Ohrbach and Dworkin, 2016). Temporomandibular disorders are also becoming more common in adolescence (Hongxing *et al*., 2016) and adulthood, with a prevalence ranging from 4.9% to 60% (Adern *et al*., 2014; Campos *et al*., 2014; Sampaio *et al*., 2017). The largest part of this group of patients is made up of women, and this has been explained by the interaction of factors such as biological, hormonal, psychological, and social (Madani *et al*., 2013; Murphy *et al*., 2013; Patil *et al*., 2015), with only a few individuals seeking treatment (Ahmad and Schiffman, 2016). The etiopathogenesis of TMD remains unclear. In general, it is thought that the origin of TMD is multifactorial, including biomechanical, neuromuscular, biopsychosocial, and biological factors developing from predisposing factors and/or perpetuating factors (Chisnoiu *et al*., 2015; Prasad *et al*., 2016). There is still no consensus in the literature for diagnostic criteria, which is usually performed on the basis of symptoms, physical examination, and imaging examination (Hunter and Kalathingal, 2013; Gauer and Semidey, 2015). To standardize these criteria and make them valid and universal; a proposal by Dworkin and LeResche (1992a), which is a Research Diagnostic Criteria (RDC/TMD), was developed in the form of a self-administered questionnaire, with reliable and valid criteria. Through two axes, the complex interaction of physical and mental symptoms of TMD is examined. Axis I allow for the evaluation of physical symptoms and a reduction in the amplitude of movements by clinical examination, resulting in the classification of TMD into three groups: (1) muscle disorders, including myofascial pain, with and without mouth opening limitation; (2) displacement of the disk, with or without a reduction or limitation in mouth opening; and (3) arthralgia, arthritis, and arthrosis. Axis II assesses functional jaw disability, psychological status, and psychosocial functioning. The RDC/TMD is a dual-axis system, which has been adopted worldwide as a standard for the evaluation of TMD (Manfredini *et al*., 2011). The use of RDC/TMD axis II is very important since around 75 % of patients with TMD suffer from chronic symptoms (Manfredini *et al*., 2011), with negative biopsychosocial consequences such as depression and somatization (Ohrbach *et al*., 2010). Human involvement (principally clinicians and patients) is one of the key limitations in conventional diagnostic procedures (Gauer and Semidey, 2015). These limitations may lead to inaccuracy and misidentification of some of the symptoms. Developing better approaches is therefore necessary to allow for broad screening of TMD and accurate identification of individuals with or without the condition, which may lead to progress in the field.

Furthermore, recognition of the relationship between TMD and increased levels of biochemical or inflammatory markers allows for the exploration of more sensitive and new biomarkers in this area (Poluha and Grossmann, 2018). Although many synovial, serum, and urinary proteins demonstrate useful diagnostic value for TMD, no perfect and direct package of disease markers for TMD is being used as a daily activity in medical practice. However, there is sufficient progress being made, which demonstrates the attempts to perform a detailed assessment of this area and future directions of research based on the accumulated evidence (Zwiri *et al*., 2020a). Cytokines are the crucial polypeptides that act as moderators of serious and severe inflammatory processes (Muñoz-Carrillo *et al*., 2018). In general, studies showed that the most likely possible TMD biomarkers were IL-6, IL-8, IL-1, and TNF (Zwiri et al., 2020a). Furthermore, the level of C-reactive protein (CRP) in TMD patients with chronic pain was also evaluated (Pihut *et al*., 2018). However, inconsistent literature findings even when the same test methods were used have been recorded. These findings make it difficult to compare the diagnostic and prognostic capacities of these biomarkers. The biomarker profile of patients with TMDs, as a critical part of the diagnostic process, is still in need of further research to identify gold standard biomarkers (Zwiri *et al*., 2020a). Most patients seek treatment for pain, whether it is mild, moderate, or severe, which can be referred to, in addition to the TMJ region, in the head, neck, ears, and eyes (Prasad *et al*., 2016). In order to be able to respond directly to the needs of the individual patient, a multidisciplinary team management approach is necessary for the fundamental treatment of all TMD patients (Dimitroulis, 2018; Xu *et al*., 2018). Depending on the severity of the case and contributing factors defined for each patient, treatment plans should concentrate on pain experience, jaw and psychosocial functioning and not solely on local mechanical factors (e.g., jaw position) (Kapos *et al*., 2020). Treatment progress from one modality to another occurs only after more conventional treatment methods have failed and after subsequently moving to the least invasive and reversible therapies. More invasive and sometimes non-reversible procedures should be undertaken only after a failure to change the progression of the disease and relevant symptoms (Liu and Steinkeler, 2013). Treatment objectives in TMD patients are pain control, recovery of function, prevention of more joint injury, improving quality of life and minimizing disease-related morbidity (Gupta et al., 2019). Conservative "reversible" management of TMD remains the most common approach to the management of more than 90% of patients (Ahmad and Schiffman, 2016). Psychological (Randhawa *et al*., 2016; Gil-Martnez *et al*., 2018), splints (Ahmad and Schiffman, 2016; Al-Moraissi *et al*., 2020), pharmacological therapies (HäggmanHenrikson *et al*., 2017; Dimitroulis, 2018), physiotherapy (Calixtre *et al*., 2015; Paço *et al*., 2016), Irreversible treatment involves orthodontics, occlusal adjustments (Manfredini, 2018; Manfredini *et al*., 2017), and surgery (Dimitroulis *et al*., 2018). A key component of primary non-invasive treatment is known as 'self-care' or 'self-management’ (SM). Self-care or SM can be all that is needed for people who are responsive or enthusiastic or can be part of a more complicated approach (Durham *et al*., 2013; Durham *et al*., 2016). Such SM techniques are often very important for giving patients some control over monitoring their symptoms when they have long-term TMD attacks or flare-ups, in addition to the first treatment (Kapos *et al*., 2020). According to a recent systematic review (Pimentel *et al*., 2018) that looked at the effectiveness of SM approaches, SM is not only low-tech and non-invasive, but it is also effective in reducing pain and enhancing functions. However, the efficacy of SM as a stand-alone treatment was not yet known, as it was typically the comparator treatment and was not correlated with any treatment or control groups (Durham *et al*., 2016). Therefore, further research is needed to confirm that SM programs are more beneficial than no treatment and/or placebo at all. With more standardized SM programs, greater clinical results could be achieved, and it would definitely be easier for clinicians to repeat successful interventions if SM programs reported in the literature described their modules with the use of established behavioural change categorisation (Story *et al*., 2016). Among all the non-surgical treatments for TMD, LLLT has recently been put on the spot because its proponents claim its easy application, limited treatment time, and minimum contraindications (Chen *et al*., 2015). The word "LASER" is an abbreviation for light amplification by stimulated emission of radiation. In dentistry, lasers are considered a new technology utilized in clinical dentistry, overcoming some of the disadvantages of classical dental therapies (David and Gupta, 2015). Shukla and Muthusekhar (2016) used LLLT to alleviate the signs and symptoms of TMD patients based on its biostimulative, regenerative, analgesic, and anti-inflammatory effects (Shukla and Muthusekhar, 2016). However, the application criteria, such as the type of TMD, as well as the choice of parameters, such as intensity and frequency, need to be homogenized in order to establish definitive conclusions (Chen *et al*., 2015). No definitive conclusions can be drawn on the efficacy of LLLT for the treatment of TMD. Many methodological differences among the studies do not allow for standardized guidelines for effective treatment with LLLT (Shukla and Muthusekhar, 2016; Xu *et al*., 2018; Zokaee *et al*., 2018). Therefore, further well-designed studies are needed (Munguia *et al*., 2018).

1.2 Problem statement

Although TMD is prevalent among Asians and Malaysians (50.9%) (Bahar *et al*., 2021), its treatment modalities involving SM and LLLT have not been widely investigated. Over the past recent years, a number of systematic reviews with or without meta-analysis have analysed the efficacy of LLLT for TMD. However, there is no solid evidence to support or refute LLLT for TMD (Xu *et al.*, 2018), although its potential exists.

No previous studies have investigated the effect of treating TMD using LLLT and comparing it with standard conservative treatment as accepted, affordable, and non-invasive treatments. There are also no previous studies investigating the effect of these treatment modalities on TMJ biomarkers. To study TMJ biomarkers, it is very difficult to aspirate the proper amount of synovial fluid from a small joint, even though recent advances in arthroscopic surgery allowed the direct examination of the TMJ. In both situations, the special equipment and biochemical components are necessary, so it is difficult to apply those procedures in daily practice. Blood serum is currently the gold standard for discriminatory biomarker discovery and validation with high sensitivity but still specificity is variable. Traditionally, blood serum has served as the most commonly accessed biofluid for the molecular diagnosis of systemic disease as well as certain orofacial conditions (Katsiougiannis *et al.*, 2017).

1.3 Justification of study

There is a growing need for effective, reliable, and patient accepted treatment modalities to overcome the unmet patients' needs and expectations regarding the treatment of TMD. Countless efforts and research have been made to overcome this problem, but because of the unclear and complex pathophysiology and aetiology of this condition, more efforts and research should be done to explore their relationship. We aim to produce an effective treatment model for TMJ pain that can be used in the clinic, which will help TMD patients address their concerns and improve their quality of life. One more important reason for this study is to have a clear treatment protocol that can be followed by physicians treating TMD and monitoring treatment through assessment of biomarkers.

1.4 Research objectives

General objective

To compare the effect of treating TMD by low level laser therapy (LLLT), standard conservative treatment (home based therapy) and the combination treatments.

Specific objective

1. To compare biomarkers (IL-6, IL-8 and highly sensitive C reactive protein Hs-CRP) and clinical parameters (anxiety level, psychosocial factors, jaw movements and pain intensity) before and after LLLT treatment of TMD among patients at Dental Clinics, School of Dental Sciences, USM.
2. To compare biomarkers (IL-6, IL-8 and highly sensitive C reactive protein Hs-CRP) and clinical parameters (anxiety level, psychosocial factors, jaw movements and pain intensity) before and after standard conservative treatment (home based therapy) of TMD among patients at Dental Clinics, School of Dental Sciences, USM
3. To compare biomarkers (IL-6, IL-8 and highly sensitive C reactive protein Hs-CRP) and clinical parameters (anxiety level, psychosocial factors, jaw movements and pain intensity) before and after combined LLLT and standard conservative treatment (home based therapy) of TMD among patients at Dental Clinics, School of Dental Sciences, USM

1.5 Research questions

1. Is there any difference in the biomarkers (IL-6, IL-8, and Hs-CRP) and clinical parameters (anxiety level, psychosocial factors, jaw movements and pain intensity) in TMD patients receiving LLLT treatment?
2. Is there any difference in the biomarkers (IL-6, IL-8, and Hs-CRP) and clinical parameters (anxiety level, psychosocial factors, jaw movements and pain intensity) in TMD patients receiving standard conservative treatment?
3. Is there any difference in the biomarkers (IL-6, IL-8, and Hs-CRP) and clinical parameters (anxiety level, psychosocial factors, jaw movements and pain intensity) in TMD patients receiving combined LLLT and standard conservative treatment?

1.6 Research hypotheses

The alternate hypotheses are:

1. Patients with TMD who receive LLLT will have significant positive changes in their biomarkers (IL-6, IL-8, and Hs-CRP) and clinical parameters (anxiety level, psychosocial factors, jaw movements and pain intensity).
2. Patients with TMD who receive standard conservative treatment will have significant positive changes in their biomarkers (IL-6, IL-8 and Hs-CRP) and clinical parameters (anxiety level, psychosocial factors, jaw movements and pain intensity)
3. Patients with TMD treated by a combination of LLLT and standard conservative treatment will have significant positive changes in their biomarkers (IL-6, IL-8 and Hs-CRP) and clinical parameters (anxiety level, psychosocial factors, jaw movements and pain intensity)

Chapter 2
LITERATURE REVIEW

2.1 Pain and orofacial pain

Pain is an unpleasant sensory and emotional experience connected with or explained in terms of actual or potential tissue damage if there is no physical derangement (IASP, 2017). The function of pain is to protect the body from potentially harmful events by stimulating the body and promoting healing by facilitating movement sensitivity or other stimuli that can impede recovery. However, pain is not always associated with tissue damage and does not always serve as a defensive mechanism. It relates to neuropathic pain caused by damage or disorder of the nervous system's somatosensory components and other chronic pain conditions such as fibromyalgia and migraine (Treede *et al.*, 2019).

Acute and chronic pain may cause distress and interfere with daily life and influencing treatment decisions (Finnerup, 2019). Chronic pain has a significant impact on the patient's regular activities and quality of life as well as on the patient's social and family life (Dueñas *et al*., 2016). Acute pain is the most common presentation following surgery (Buvanendran et al., 2015). Acute pain, which is common in primary care and other hospital setting is the most common reason for emergency room visits (Cordell *et al.*, 2002; Dix *et al.*, 2004; Henschke *et al.*, 2015).

The biopsychosocial model for pain (Figure 2.1) provides a framework for identifying how different symptoms are associated by assessing sensory, cognitive, and interpersonal factors (Scott *et al.*, 2007). This model is particularly useful in the orofacial zone, where the individual has unique biological, emotional, and psychological characteristics (Vaughn *et al.*, 2019). Pain is a complex subjective phenomenon dependent on gender, age, culture, and experience (Marchand, 2015).

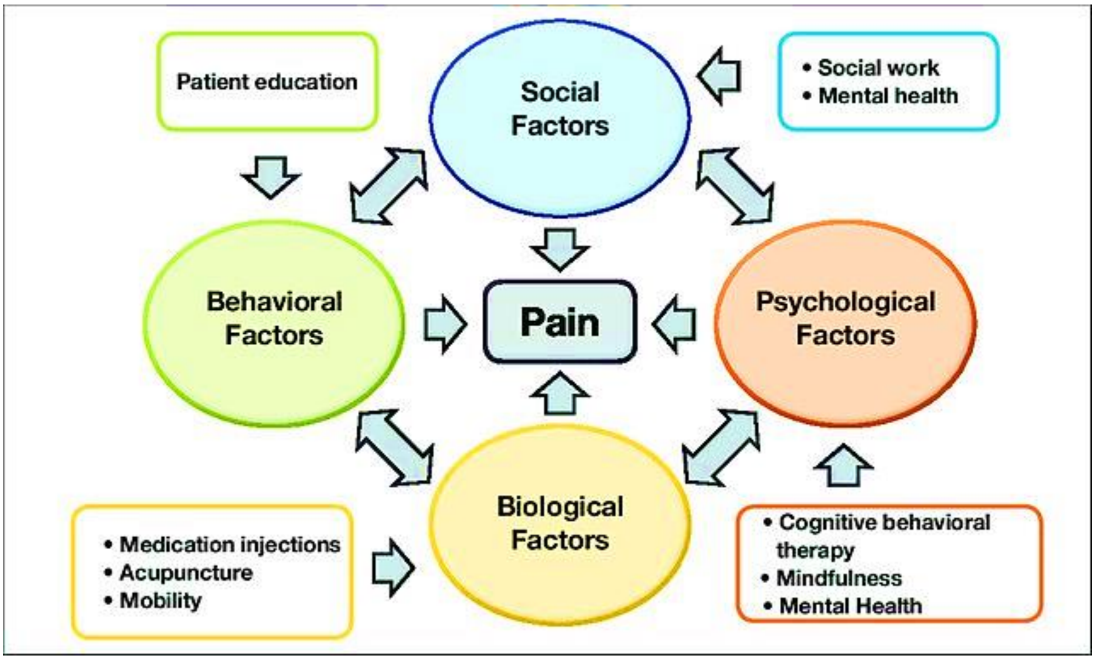


Figure 2.1: The biopsychosocial model of pain (Adapted from Vaughn *et al.*, 2019).

Orofacial pain is defined as pain that is manifested in the face or oral cavity, including disorders such as TMD, which is a major cause of nonodontogenic orofacial pain (Gupta *et al.*, 2016). Orofacial pain disorders are common and distressing that affect the head, face, and neck conditions. Since the orofacial region is full of complex structures, pain can occur from multiple causes, that poses a challenge to the clinician. For optimal care, the clinician must have a thorough knowledge and understanding of the pain conditions that arise from these structures, and a multidisciplinary management plan is strongly recommended (Romero-Reyes and Uyanik, 2014).

2.1.1 Physiology of pain

Pain mechanisms can be classified as peripheral (nociceptive, neuropathic) and centralized (Figure 2.2). Although this classification system excessively simplifies the broad variety of potential mechanisms within each group, it does provide a method for physicians to limit care options based on the most common signs and symptoms of each patient. While certain conditions of chronic pain like fibromyalgia are considered as centralized, others like osteoarthritis came into more peripheral. However, still no pain diagnosis fits neatly into a single mechanistic group. Moreover, there is no recognized chronic pain illness in which the degree of peripheral injury reproducibly causes the same level of pain across individuals as observed. Also, there is no exception in TMD. The distinction between centralized and peripheral pain is important, as its prognosis and treatment could be influenced by the pain mechanism (Harper *et al.*, 2016).

	Causes	Signs & Symptoms	Treatments	Classic Examples
Peripheral Nociceptive	Stimulation of nociceptors due to potential or actual tissue damage, inflammation	Localized pain & tenderness at or near injured area No widespread hyperalgesia Perceived intensity varies with amount of nociceptive stimulation within individual, but differs across individuals	NSAIDs, acetaminophen, opioids, anti-inflammatories Procedures to target peripheral damage/inflammation (e.g. knee arthroplasty, occlusal splint, etc.) Pain goes away when nociceptors are no longer stimulated	**Acute:** broken bones, contusions, surgery **Chronic:** Osteoarthritis, rheumatoid arthritis, cancer pain
Peripheral Neuropathic	Damaged or dysfunctional primary nociceptive afferents	Pain usually referred to dermatomal area innervated by damaged nerve(s); also sometimes felt near nerve damage (e.g. sciatica) No widespread hyperalgesia, unless nerve damage is diffuse Pain can be radiating, shooting, highly variable	Opioids (though not recommended for chronic pain), some centrally acting drugs Procedures to target peripheral pain transmission (e.g. nerve block) Pain goes away with nerve healing in some cases, but other cases damage (and pain) more permanent	Trigeminal neuralgia, post-herpetic neuralgia, diabetic neuropathic pain
Centralized	Dysregulated pain-processing circuitry in the spinal cord and/or brain Could involve structural, functional, and/or metabolic (e.g. neurotransmitter) aberrations	Pain can be regional or diffuse, usually not as well-localized Widespread hyperalgesia, high somatic awareness, and multisensory sensitivity No correlation between amount of peripheral damage and perceived pain Often comorbid with other chronic conditions	Centrally-acting drugs (e.g. gabapentin, pregabalin, tricyclics, SNRIs), cognitive-behavioral therapy, pain coping skills Does NOT usually respond well to opioids Does NOT respond as well to peripherally-targeted treatments Complete pain relief in some cases, but for most the focus should be management	Fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, chronic pelvic pain, TMD (many chronic cases)

Figure 2.2: Pain mechanisms (adapted from Harper *et al.*, 2016).

Nociceptors are receptors that are directly activated by painful stimuli in tissues. The receptors process this 'noxious' information into an electrical signal and transfer it through axons from the periphery to the central nervous system (Steeds, 2016). Two types of nociceptors are available: high-threshold mechanoreceptors (HTMs) reacting to mechanical distortion and polymodal nociceptors (PMNs) responding to a variety of tissue-damaging inputs, such as 5-hydroxytryptamine (5-HT), bradykinin, cytokines, histamine, prostaglandins, and leukotrienes (Kendroud *et al.*,2020). These inflammatory mediators, who activate and sensitize them, storm the nociceptors. Through stimuli of low intensity, prostaglandins and bradykinin make nociceptors responsive to activation. Nociceptors are, therefore, the free ends of nerve fibers. There are 2 primary categories of fibers: A-delta (myelinated, small diameter, slowconducting) and C-fibers (unmyelinated, smaller-diameter, much slower-conducting) (Schnakberg *et al*.,2021). Either in the dorsal root ganglia or the trigeminal ganglion, these primary afferent nerve fibers have cell bodies and end up in the dorsal horn of the spinal cord. They travel just lateral to myelinated A-beta fibers with a larger diameter that respond to non-painful stimuli such as vibration and light touch (Steeds, 2016)**.**

The term "central pain" has generally been used to explain the condition of patients with chronic pain because of extensive damage to the central nervous system, such as stroke or injury, as an example of thalamic pain syndrome. More recently, the term central sensitization has been used to describe the amplification of pain signals that may happen in chronic pain (Harper *et al.*, 2016). Centralized pain is common in a variety of chronic idiopathic pain disorders, including fibromyalgia (FM), chronic fatigue syndrome (CFS), irritable bowel syndrome, headache, TMD, and interstitial cystitis (Clauw, 2014).

Since mechanical nociceptor stimulation increases neuropeptide release and inflammatory mediators in the TMJ pain area, and because excessive TMJ loading can set off peripheral mechanisms such as these, pain is triggered in the area. Prolonged central nervous system sensitization appears to result in persistent nociceptive feedback from painful TMJ. Lower TMJ pain levels and resistance are thought to contribute to this central sensitization. There is no clear evidence in myofascial pain that masticatory muscle tone is increased to the extent that would cause painful muscle spasms in these patients. Masticatory muscle pain may be triggered by inducing localized tissue ischaemia and/or releasing substances such as serotonin or glutamate to stimulate and sensitize muscle nociceptors. Parafunctional activities such as clenching or grinding of teeth can cause repeated strain injury to the muscle. Continuous masticatory muscle pain is also effective at causing central sensitization, which may explain the peculiar pain referral patterns associated with this type of pain (Cairns, 2010).

2.1.2 Epidemiology of orofacial pain

Accurate estimates of the incidence of facial pain in the general population are vague. Up to 26% prevalence has been reported by Macfarlane *et al.* (2002). Macfarlane *et al.* (2014) reported a 1.9% incidence of facial pain in the United Kingdom, of which 48% was reported as chronic. These findings are significant because chronic persistent orofacial pain can cause anxiety, physical disability, and negative psychosocial consequences (Bonathan *et al.*, 2014; Shueb *et al.*, 2015). According to the findings of international epidemiological studies, orofacial pain affects about 10 % of the adult population, with greater female predilection and a decline in excess prevalence (Shetty *et al.*, 2015). A study reported pulpitis as the most prevalent cause for orofacial pain among 43% of patients attend in general dental practice, followed by 32% of patients having periodontal pain as a reason for orofacial pain;13% had pericoronitis as a cause of pain, while TMD and neuralgia were affected only 8% of the patients (Shetty *et al.*, 2015). In the general population, orofacial pain conditions are very prevalent, and their impact on quality of life. There is insufficient available epidemiological evidence from the existing literature for subtypes of pain-producing diseases in the orofacial region. To establish effective treatment strategies, clinicians should be aware of the broad range of diseases that cause painful symptoms in the orofacial zone (Setty and David, 2014).

2.1.3 Pain measurements

Measuring pain is almost impossible. The perception of pain is determined by the individual’s response which is based largely on one’s own experience of pain and is not reproducible by others. The estimation of pain is an integral aspect of any medical examination, including diagnosis, monitoring of disease progression, and assessment of treatment efficacy. Unfortunately, there is no single common or simple form for pain measurement. Since pain is a personal and private experience, indirect, self-reporting, physiological, and behavioural approaches are therefore used in the methods to measure pain (Eliav and Gracely, 2008; Egbuniwe and Renton, 2015). Pain can be described using various specific characteristics or features such as quality, location, intensity, emotional impact, frequency, etc. (Caraceni *et al.*, 2002).

Pain measurement is crucial in pain research. It is important to determine whether a new pain management approach is superior to another, as well as the degree of disability or loss of pain-related functioning for therapeutic or compensatory purposes (Ong and Seymour, 2004). However, in the modern era of evidence-based medicine, clinicians and researchers must use pain outcome measures that is responsive and precise. At present, there is no clear and accurate tool for quantifying an individual's pain experience. Thus, we are dependent primarily on self-reporting measures to assess the impact of pain (Younger *et al.*, 2009). A variety of pain measurement methods have been developed for use. However, only the most frequently used and validated tools are presented.

2.1.3(a) Unidimensional scales

In the busy clinical setting, pain measurement needs to be simple, quick to administer, and easily understood by the patient. Unidimensional scales fulfil this role by allowing pain measurement to be performed quickly and multiple times with minimal operational effort (Younger *et al.*, 2009). Unidimensional scales include:

Verbal rating scale (VRS)

VRS is used for people who have difficulty explaining their experience of pain into a numerical value. Instead, presenters are substituted by descriptors for the various pain intensity levels, such as no pain, mild pain, moderate pain, and extreme pain which are labelled on a four or 15-point scale and have been shown to be simple to administer and valid as measures of pain intensity (Jensen *et al.*, 1989; Pathak *et al.*, 2018). A drawback of having rank scoring is that it accepts equal intervals between adjectives, while equal intervals are unlikely to occur. The second problem is that VRS for scaling are ordinary data. Grade scores on the verbal scale are often viewed as data on the interval or ratio and then evaluated using parametric statistical techniques rather than suitable non-parametric methods. The third issue is that it lacks sensitivity and does not allow finer-grade pain assessments (Ong and Seymour, 2004). Good to have a conclusion regarding VRS, whether good or not.

Numerical rating scale (**NRS)**

In this method, patients are asked to rate their pain intensity from 0 (no pain) to a 10-point scale or 100-point scale (unbearable). Patients' pain intensity is estimated by the number that patient notes. It is a reliable and simple method with a positive significant correlation with other pain intensity measures (Jensen *et al.*, 1989; Turk and Melzack, 2011; Pathak *et al.*, 2018).

Visual analogue scale (VAS)

The VAS method is most commonly used to measure the severity of the pain and comprises of a line which is usually 10 cm long (Eliav and Gracely, 2008). Patients indicate their intensity of pain along the lines. The pain level difference ranges from the "no pain" to the mark of the individual's response, which is the pain severity. Pain-affect VAS was designed to integrate areas other than the sensory severity aspect of the observable pain experience. The main advantage of VAS is its simplicity. It is widely used and language independent. Most patients understand it quickly, and readily can be repeated on successive presentations (Ong and Seymour, 2004). VAS has been validated in several studies (ChoiniÈre *et al.*, 1989; Rosier *et al.*, 2002; Pathak *et al.*, 2018). It applies to both drug and non-drug treatments that affect the pain perception (Joyce *et al.*, 1975; Seymour, 1982). The level of pain intensity on the VRS and NRS are often correlated (Jensen *et al.*, 1986; Ham et al., 2015; Thong *et al.*, 2018). VAS is a ratio scale-based that can be statistically interpretable. VAS responses need visual and motor coordination and are affected by many different factors influencing psychophysical responses like anaesthesia (Ong and Seymour, 2004). The VAS can be used as a graphical scale on paper or electronically. Paper VAS are strongly associated with electronic VAS (Jamison *et al.*, 2002). The VAS has high resolution and is potentially the most sensitive measure for the best suitable response in clinical pain.

2.1.3(b) Multidimensional pain scales

Adequate pain management is a form of social interaction between the patient and the caregiver. Pain management should be guided by the various aspects of the pain experience. In many cases, a simple, one-item instrument is insufficient to identify pain or quality of life (van Boekel *et al.*, 2017). There are many comprehensive instruments for measuring pain. These instruments usually measure different aspects of pain, including the severity of pain, consistency, impact, functioning interferences, and effects on general quality of life. Such scales will address the widely observed lack of correlation between pain severity and disability by measuring the pain in a more comprehensive way (Younger *et al.*, 2009). The most used multidimensional pain scales are:

McGill Pain Questionnaire

This questionnaire was developed by Professor Melzack of McGill University. The purpose of this questionnaire is to investigate three dimensions of the pain perception report: sensory, adaptive, and interpretative. It consists of 87 descriptors of the pain's sensory attributes and associated feelings, as well as a line drawing of the body in which the patient outlines pain position with the overall pain intensity score (Melzack, 1975). The McGill Pain Questionnaire short form (SF-MPQ) is a concise, validated instrument with extensive use in clinical studies. The SF-MPQ has 15 total descriptors of sensory terms (e.g., painful or stinging) and affective terms (e.g., sickening, or scared) to measure patients' pain intensity. The scale of each object is 4 points, varying from no to severe. The SF-MPQ also includes a specific VAS feature as well as a VRS for overall pain rating (Melzack, 1987).

Specialized psychological tests

The tests were designed to interpret the pain experienced in the context of a patient's life. This assessment usually involves at least one interview and the administration of one or more psychological self-reporting measures. The following are the most common biopsychosocial models:

(i) Psychosocial pain index (PSPI)

It is the most well-known standardized chronic pain interview, which collects information on 25 psychosocial dimensions of chronic pain (Burns *et al.*, 2009).

(ii) Brief pain inventory short form (BPI-SF)

This covers two specific pain domains: 1) the perceived severity of pain, and 2) the degree to which pain interferes throughout life. These 17 scale items also measure the position of pain, pain medication usage, and treatment response (Dana *et al*., 2020).

(iii) Minnesota multiphasic personality inventory (MMPI)

The MMPI categorizes patients according to types of personality that are associated with severe pain experiences; however, it isdifficult to conduct (Bradley and McKendree-Smith, 2001).

(iv) Beck depression inventory This is perhaps the most widely used instrument in pain studies (García-Batista *et al.*, 2018). It is a questionnaire made up of 21 sets of items. Each set of items is ranked by severity and scored from 0 to 3. It is the most validated instrument across different populations and countries (Dana *et al*., 2020)

2.2 Temporomandibular joint disorder

Temporomandibular joint disorder (TMD) is a universal term for illnesses of the temporomandibular joint (TMJ) and the muscles of the orofacial region (Sari and Sonmez, 2002; Poveda Roda *et al*., 2007; Huang *et al*., 2014). Luther (1998) used the term TMD to indicate the range of symptoms, signs and their consequences attributed to the TMJ and its associated structures. Temporomandibular disorders (TMDs) are defined by the American Academy of Orofacial Pain as a collective term that includes several clinical problems involving masticatory muscles, temporomandibular joint (TMJ) and associated musculoskeletal structures of the head and neck (Scrivani *et al.*, 2008). These may be associated with or without restrictions and/or movement deviations (El-Warrak *et al.*, 2011), joint noises (clicking or grating sounds) and chewing difficulty (Núñez *et al.*, 2006; La Touche *et al.*, 2009). At present, clinicians are unable to agree on a precise definition of TMD (Zwiri and Al-Omiri, 2016).

Temporomandibular disorder is a diverse group of diseases that affect TMJ, muscles of the jaw, or both (Shaffer *et al.*, 2014a). Therefore the term TMD could be considered as a gamp for several clinical findings affecting TMJ and mastication muscles (Ryalat *et al.*, 2009). To overcome diagnostic difficulties and achieving correct treatment, which is already controversial, thorough knowledge is essential. Besides, TMD findings can vary between individuals and within the same individual at different times, which further complicates the diagnosis of TMD and makes it more difficult to diagnose (Cooper and Kleinberg, 2007).

Temporomandibular disorders, however, are the most common non-odontogenic orofacial pain conditions that patients seek care for (Romero-Reyes and Uyanik, 2014; Saranya *et al.*, 2019). Therefore, TMD patients are becoming a major component of patients referred to dental clinics. TMD is a complex disease, and its existence has not yet been fully understood. Patients also have several alterations, where muscular and articular symptoms and signs intermingle, making it difficult to diagnose and ultimately treat (Tartaglia *et al.*, 2011). There are numerous causes for this condition including trauma, systemic, iatrogenic, occlusal, and mental health disorders (Kobs *et al.*, 2005; Kijak *et al.*, 2013; Liu and Steinkeler, 2013; Bono *et al.*, 2014). Mental health and psychosocial status today play a dominant part in TMD pathogenesis (Fernandes *et al.*, 2013; Calixtre *et al.*, 2014; Ghurye and McMillan, 2015).

2.2.1 Anatomy of the masticatory system

Temporomandibular articulation is considered one of the most complex joints in the body. It enables for rotational and translational movement of the mandible against the cranium. The presence of an articular disc allows the condylar head to move complexly against the glenoid fossa (Okeson, 2019).

Articular discs consist of fibrous connective tissue and are often denervated and avascular in nature. On the medial aspect, it is slightly larger and can be split into three sections: anterior, posterior, and intermediate zones. The disc attachments are posteriorly and anterior collagenous attachments to the joint capsule through the upper and lower retro discal laminae. Joint space is divided into a superior and a lower space filled with synovial fluid, which during function serves as a lubricant. The condylar head articular cartilage consists of four histologically distinct zones: articular, proliferative, fibrocartilaginous, and calcified layers. These layers are thought to be better able to withstand functional forces (compressive and lateral) and seem to be better able to repair and reshape as a result of the impact of the ageing process than hyaline cartilage (Okeson, 2019). The muscles of the jaw include the pterygoid and the masseter which helps in jaw closing, and the temporalis which responsible for the jaw closing and pulls the mandible back (Figure 2.3).

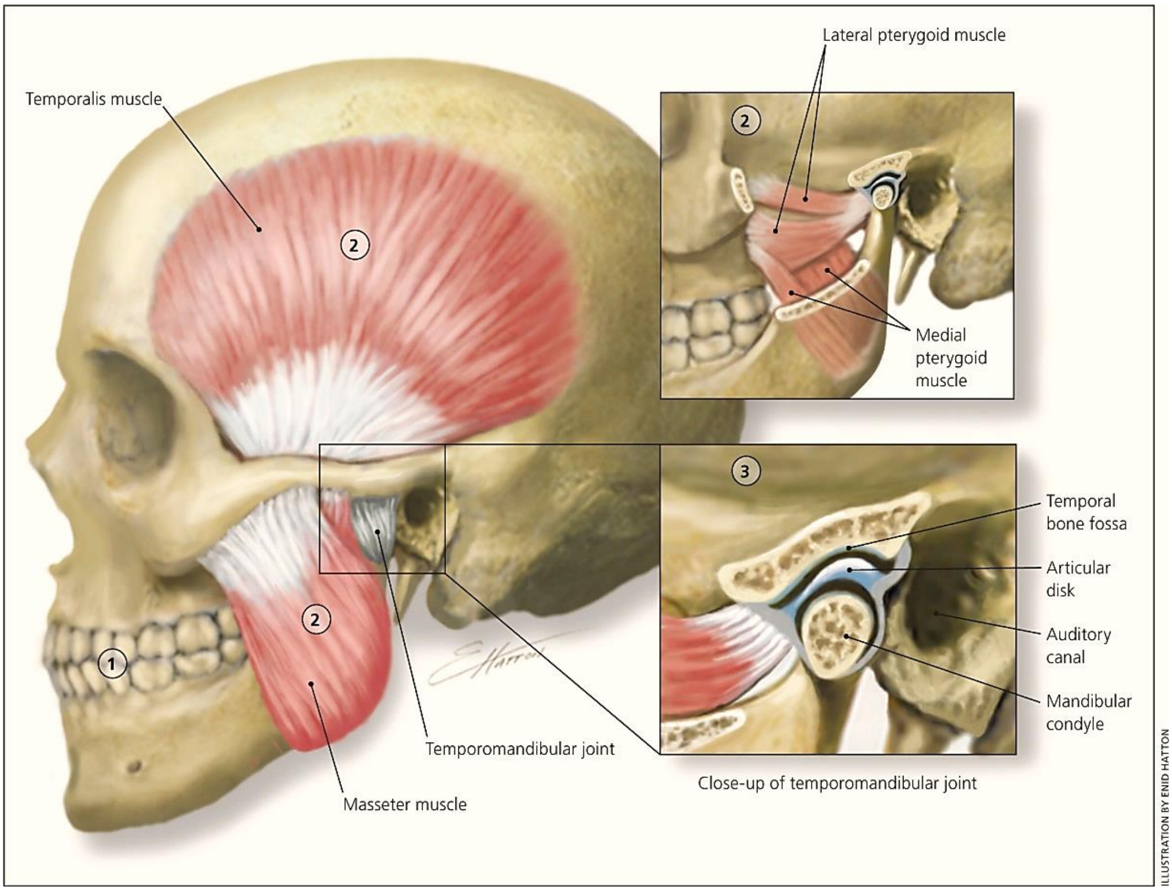
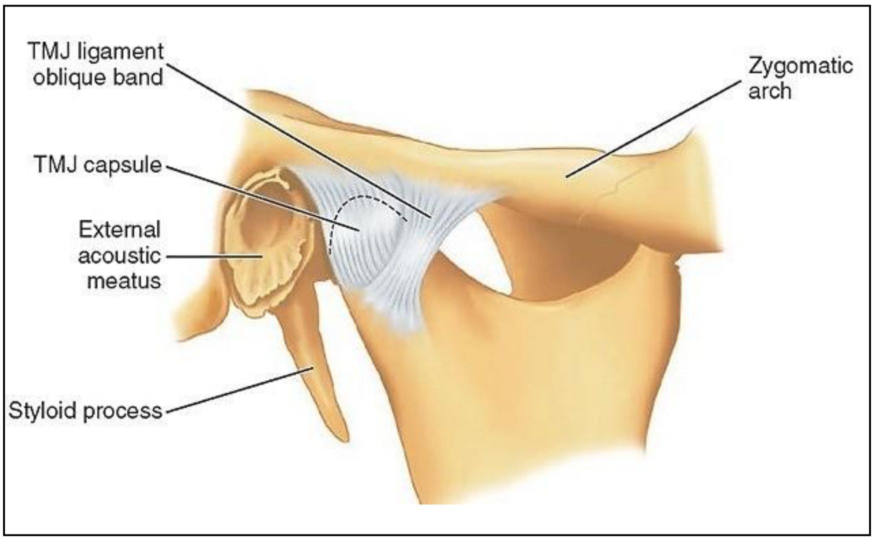


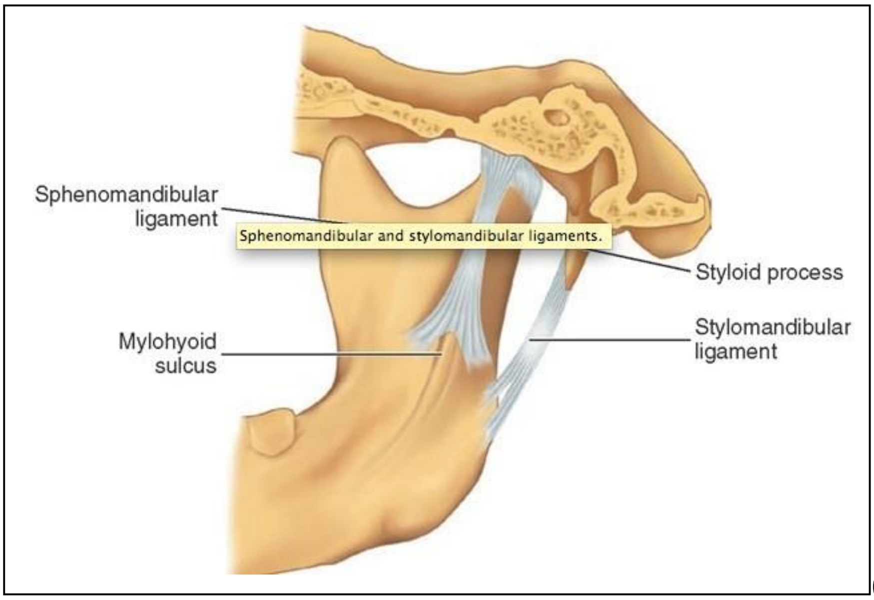
Figure 2.3. Anatomy of the temporomandibular joint and the structures responsible for the movement of the joint. 1. Teeth and mandible. 2. Muscles of mastication. 3. Temporomandibular joint (TMJ). TMJ is a gliding joint formed by the mandibular condyle and temporal bone fossa. The ligamentous capsule, articular disc, and retro discal tissue allow for smooth joint movement (Gauer and Semidey, 2015).

TMJ is innervated by the auriculotemporal nerve, the deep temporal nerve and the masseteric branches of the mandibular nerve. The blood supply of TMJ comes from the surrounding vessels: superficial temporal artery, middle meningeal artery, and internal maxillary artery. Other contributing vessels include deep auricular, anterior tympanic and ascending pharyngeal arteries (Okeson, 2019).

TMJ is surrounded by three functional ligaments, namely: collateral, capsular and temporomandibular ligaments and two accessory ligaments, which are sphenomandibular and stylomandibular. The principal role of ligaments is to suppress and limit extreme border joint movements passively (Figure 2.4).



(a)



(b)

Figure 2.4: Mandibular ligaments (a &b) (Gauer and Semidey, 2015)

2.2.2 Epidemiology

Determination of TMD’s prevalence is a complicated problem due to the regular simultaneous occurrence of other symptoms such as neuralgia, ear inflammation, headache, and dental pain that may be linked to TMD or appear as additional findings. Therefore, TMD needs to be evaluated throughout the differential diagnosis procedure (LeResche, 1997). The reported prevalence of TMD differs widely in the literature because of differences in studied populations, diagnostic criteria, testing methods, and variations of examiners (Sena *et al.*, 2013). Additionally, studies have shown that symptoms and signs of TMD are uncommon in early childhood (KÖhler *et al.*, 2009). In several countries (Canada, America, Denmark, the Netherlands, the United Kingdom, Sweden, Italy, Finland, Brazil, Iran, India, and Pakistan), epidemiological studies have shown a large prevalence of symptoms of orofacial pain in adults,