ASSOCIATON OF AUTONOMIC FUNCTION WITH TEMPOROMANDIBULAR DISORDERS

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Abstract

Masticatory muscles and temporomandibular joints (TMJs) are essential components of the masticatory system and temporomandibular disorders (TMD) is the term used for painful conditions and disturbances of the masticatory system and its related structures. The etiology of TMD is multifactorial but one of the predominant conceptions is the biopsychosocial theory yet there is a lot of interest towards the connection of autonomic function and TMD. Baroreflex and heart rate variability (HRV) are examples of autonomic variables that are controlled autonomically by the autonomic nervous system (ANS). Baroreflex regulates blood pressure whereas HRV is used to assess ANS function. This literature review reveals that higher HR, HR at rest and reduced HRV are associated with TMD. Pain perception and modulation are also found to be altered in TMD patients which appears as hypersensitivity of the nervous system. There is also evidence that dysfunction of the sympathetic nervous system function is associated with TMD and TMD subjects have altered brain function in response to certain events.

Keywords: masticatory system, temporomandibular disorders, TMD, facial pain, autonomic nervous system, autonomic function, autonomic dysfunction, cardiovascular function, cardiovascular measures, heart rate, heart rate variability

TABLE OF CONTENTS

1 INTRODUCTION

There is remarkable interest towards association of autonomic function and temporomandibular disorders (TMD). Results from numerous studies confirm that TMD patients have differences in autonomic variables compared to controls thus autonomic dysfunction is somewhat associated with TMD (Sarlani & Greenspan 2005, Vuong et al. 2020, Monaco et al. 2012, Monaco et al. 2015, Maixner et al. 2011b, Greenspan et al. 2013, Eze-Nliam et al. 2011). Yet it is unknown whether there is a cause-effect relationship between the findings and TMD or if they are a consequence of the condition. Several studies have found similar results concerning autonomic function and TMD.

The aim of this current literature review is to evaluate the association between autonomic function and TMD. This review describes the fundamentals of the masticatory system, TMD, ANS with focus on the autonomic measures, and this review presents results from various studies regarding the previous topics.

2 THE MASTICATORY SYSTEM

The maxilla, the mandible, the temporal bone, the masticatory muscles, the temporomandibular joints (TMJs), teeth attached to the alveolar bone, ligaments supporting the joints, and other associated anatomical structures are important components of the masticatory system which are in charge of vitally important functions such as mastication and speech (Okeson 2019). Functions of the masticatory system can be controlled somatically and/or autonomically. The masseter, temporalis and the medial and lateral pterygoid muscles are the muscles responsible for mastication and they are all innervated by branches of the mandibular nerve of the fifth cranial nerve (CN V) called the trigeminal nerve and blood flow is supplied by the maxillary artery.

2.1 The masticatory muscles

The strong muscle responsible for mandibular closure, the masseter, functions to elevate the mandible and participates in protrusion. It has its origin in the zygomatic arch and insertion in the lateral part of the mandibular angle and ramus and it can be divided into the superficial and deep divisions (Okeson 2019). The masseter, as the other main masticatory muscles, get its innervation from the mandibular nerve, more closely the masseteric nerve. Its blood supply comes from a branch of the maxillary artery called the masseteric artery.

The temporal muscle, or temporalis, functions to elevate the mandible and can be divided into the anterior, middle, and posterior divisions (Okeson 2019). The temporalis also participates in retrusion and lateral movement of the mandible depending on the division activated. Its origin is in the temporal fossa of the skull, and insertion in the coronoid process of the mandible. The temporalis is innervated by the deep temporal nerve and blood is supplied by the temporal arteries.

The medial pterygoid, elevating and protruding the mandible when contracted bilaterally, has two heads – the superficial and deep head (Basit et al. 2021). The superficial head extends from the maxillary tuberosity whereas the deep head from the sphenoid bone to the same insertion at the angle of the mandible. The medial pterygoid also participates in lateral movement with the lateral pterygoid muscle. It is innervated by the medial pterygoid nerve

and blood is supplied by the pterygoid branches of the maxillary artery for both medial and lateral pterygoid muscles.

The lateral pterygoid consists of two separate muscles – the inferior which participates in protrusion, depression and lateral movement of the mandible, and the superior lateral pterygoid which is active during mastication (Okeson 2019). They both have their origin at the sphenoid bone - the superior muscle at the greater wing and the inferior muscle at the lateral pterygoid plate. They have their insertions at the neck of the mandibular condyle and parts of TMJ. Innervation is provided by the lateral pterygoid nerve.

2.2 Skeletal muscle contraction physiology

Skeletal muscle consists of bundles of multinucleated muscle cells, or muscle fibers, filled with myofibrils each of which are composed of myofilaments called actin and myosin filaments (Barrett & Ganong 2012). A cell membrane called sarcolemma surrounds each muscle fiber. Actin, myosin, and other associated proteins are arranged in myofibrils as subsequent sarcomeres, the functional units of muscle cells. A motor unit, for instance, is a group of muscle fibers innervated by a single motor neuron at neuromuscular junction. According to the sliding filament theory, muscle contraction is the result of sliding of actin on myosin and the shortening of the sarcomere. Action potential is transmitted through motor neuron axon to muscle fiber which causes depolarization and action potential at the motor end plate of the muscle fiber which eventually results in muscle contraction.

Contraction begins when motor neuron axon transmits action potential to muscle fiber at the neuromuscular junction and Ca^{2+} influx to the motor neuron's cytosol results in release of neurotransmitter acetylcholine (ACh) from synaptic vesicles to the synaptic cleft (Barrett & Ganong 2012). The ACh then binds to the nicotinic acetylcholine receptors (N_M) at the motor end plate and this results in entry of Na^+ to muscle fiber's cytosol causing end plate potential. As the end plate potential reaches the threshold it causes even more Na^+ channels to open and further depolarization of the sarcolemma with the result of action potential generation along the membrane. The action potentials travel also inwards via T-tubules until they reach the sarcoplasmic reticulum where Ca^{2+} is released allowing myosin to interact with actin and the muscle to contract.

2.3 The temporomandibular joint

TMJ a bilateral joint enabling the essential movement of the mandible, comprises the mandibular condyle, the mandibular fossa of the temporal bone, the articular disc in between and supporting ligaments such as the capsular ligament (Okeson 2019). The articular disc is also attached to the superior lateral pterygoid muscle. TMJ is innervated by the auriculotemporal, deep temporal and masseteric nerves and blood is supplied primarily by the superficial temporal artery and branches from the maxillary artery.

3 AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system (ANS), which is a part of the peripheral nervous system, can be divided into sympathetic, parasympathetic, and enteric nervous systems (Barrett & Ganong 2012). It maintains the body's internal balance and regulates involuntary physiologic functions such as blood pressure and body temperature by innervating smooth muscle, cardiac muscle, and glands without conscious control. There are two neurons between CNS and autonomic target tissues – preganglionic neuron and its axon that exits CNS and postganglionic neuron synapsing at target tissues. acetylcholine (ACh) is released at the synapse between preganglionic and postganglionic neuron. Thus, the sympathetic and parasympathetic neurons connect the CNS with the visceral tissues. The axons of the sympathetic preganglionic neurons leave the spinal cord at the thoracolumbar segments whereas parasympathetic axons at the cranial nuclei and sacral spinal cord. When the sympathetic nervous system (SNS) is active it increases heart rate, releases glucose to blood by glycogenolysis and decreases peristalsis. The parasympathetic nervous system (PNS), for instance, acts the opposite. Furthermore, the tenth cranial nerve (CN X), the vagus nerve, is an important nerve of the parasympathetic nervous system regulating functions such as heart rate and digestion. The enteric nervous system, which consists of submucosal Meissner's plexus and myenteric Auerbach's plexus, is responsible for gastrointestinal function and digestion through gastrointestinal blood flow, secretion, and motility.

3.1 Neurotransmitters

ACh is released by many neurons such as the earlier-mentioned somatic motor neurons and autonomic neurons that exit the CNS, and its receptors are either nicotinic or muscarinic (Barrett & Ganong 2012). Regarding ANS, acetylcholine is released by all preganglionic neurons and postganglionic parasympathetic neurons which means that they are cholinergic. Norepinephrine (NE), that has adrenergic receptors in target tissues, is the principal transmitter of the sympathetic postganglionic division except for some vasodilator nerves and innervation of sweat glands. Adrenoreceptors are G-protein coupled receptors (GPCR) and the main subtypes in postganglionic sympathetic transmission are α_1, β_1 and β_2. As ACh is more often a local neurotransmitter, NE is released to bloodstream from the adrenal medulla of the adrenal gland from where it reaches its target organs.

Nicotinic acetylcholine receptors (nAChRs) are ionotropic ligand-gated channels (Barrett & Ganong 2012). Nicotinic N_N receptors are responsible for the transmission between preganglionic and postganglionic neurons whereas N_M receptors are found at found the synapse between motor neuron and skeletal muscle fiber. Muscarinic acetylcholine receptors (mAChRs) are GPCR, and they mediate mainly postganglionic parasympathetic transmission of ANS.

3.2 Baroreflex

Heart function is under sympathetic and parasympathetic control (Barrett & Ganong 2012). Baroreceptors are mechanoreceptors, arterial high-pressure baroreceptors in the carotid sinus and aortic arch and cardiopulmonary low-pressure receptors in the atria and pulmonary vasculature. They provide information to central nervous system (CNS) about blood pressure (BP) and blood volume – when BP is increased and vessels are stretched, neural impulses to the nucleus of the tractus solitarius (NTS) in the brain stem result in decreased sympathetic innervation and increased vagal parasympathetic innervation of the heart resulting in vasodilation and ultimately decreased BP. This negative feedback loop, or baroreflex, works the opposite when BP is decreased, thus it adapts to maintain cardiovascular stability.

3.3 Heart rate variability

Heartbeats are generated in the SA node of the right atrium as electrical impulses. Heart rate variability (HRV), the variation in time between each heartbeat, reflects the influence of ANS on heart function thus it can be used to assess ANS function (Shaffer & Ginsberg 2017). It is essential for the cardiovascular system be able to adapt to changing circumstances and therefore HRV is not invariable. HRV is commonly examined with electrocardiogram (ECG), and it can be analyzed as short-term, ultra-short-term or long-term 24-hour HRV. Time-domain, frequency-domain and non-linear measurements are used to quantify HRV. Short-term HRV is influenced by ANS, and baroreflex and respiration. 24-hour HRV recordings reflect the effect of physiological processes such as metabolism on cardiac function. Time-domain measures, such as SDNN, determine HRV during a certain time period whereas frequency-domain measures comprise ultra-low frequency (ULF), very-low

frequency (VLF), low-frequency (LF) and high-frequency (HF) bands. The HF and LF bands are commonly used since the HF band is associated with parasympathetic nervous system while the LF band reflects both sympathetic and parasympathetic activity.

4 TEMPOROMANDIBULAR DISORDERS

TMD stand for a musculoskeletal condition comprising pain and functional disturbances of the masticatory muscles, TMJs, or both and other associated anatomical structures (Okeson 2019). That is, the disorders can be classified as muscle or joint related or combination of both. There is no single specific etiology behind TMD – there is a conception of perpetuating, initiating and predisposing factors. There are multiple etiological factors contributing to TMD, thus the biopsychosocial model is highly emphasized (Suvinen et al. 2005). Another perspective based on literature comprise trauma, stress, deep pain input, occlusal factors, and parafunctions as etiological factors for TMD (Okeson 2019). The prevalence of TMD varies in literature yet single signs and symptoms are very common. According to recent studies, TMD symptoms increase from age 20 onwards, the highest prevalence is seeing at middle age and the symptoms are more common in women than men (Lövgren et al. 2016).

TMD patients often suffer from comorbidities, the presence of multiple pain conditions at the same time, such as headache, pain in the neck, shoulders, back, joints, chronic fatigue syndrome (CFS) and fibromyalgia which is a syndrome with various symptoms including fatigue and widespread chronic pain in various bodily sights (Ayouni et al. 2019, Plesh et al. 2011, Robinson et al. 2015, Sipilä et al. 2011). Women are more likely to suffer from fibromyalgia and more susceptible to multiple comorbid pain conditions simultaneously than men. Patients with CFS can also suffer from a variety of symptoms – severe chronic fatigue, muscle and joint pain, headache, and malaise (Robinson et al. 2015). Fibromyalgia, CFS and TMD are thought to be characterized by some degree of ANS dysfunction. Patients with comorbidity of TMD and CFS may have increased activity of the parasympathetic nervous according to HRV measurements.

4.1 Signs and symptoms

There is a vast array of signs, specific and non-specific symptoms among patients with TMD (Purentaelimistön kipu ja toimintahäiriöt: Current Care Guidelines, 2021). Common TMD symptoms include unilateral or bilateral pain in masticatory muscles and/or TMJs, clicking or crepitus and disturbances in mandibular movement. The pain is usually dull, affected by

jaw function, and it varies from mild to severe pain. Non-specific symptoms include different kind of pain and sensations around face and head. Also, neck, shoulder and tooth pain or tenderness are also commonly seen in TMD as well as loss of normal tooth morphology caused by heavy occlusal forces (Okeson 2019). Heavy bruxism can also cause inflammation of the pulp in extreme cases.

Myalgia refers to muscle pain which is considered a common complaint of patients with TMD (Okeson 2019). Patient might feel muscle tenderness, fatigue, and pain during functional activity such as chewing. Local myalgia refers to acute noninflammatory local muscle pain which can result for example from muscular overuse. Myofascial pain is a CNS-influenced source of muscle pain with pain-inducing trigger points. Referred myofascial pain is felt outside the muscle area. Thus, muscle pain can originate from peripheral tissues or from the CNS. Additional to muscle pain, one can also suffer from muscle dysfunction for example disturbances in mandibular movement.

TMD signs and symptoms can also result from TMJ function (Okeson 2019). In disc displacement with reduction the first click is heard when the condyle moves from the unusual posterior surface of the disc to the optimal intermediate zone during jaw opening. Normal function occurs until the end of closing when the condyle moves back to the posterior surface of the disc and a second click can be heard. In disc displacement with reduction with intermittent locking the displaced disc can be positioned spontaneously into normal position by the patient. If the articular disc is constantly placed anteriorly, the condition is called disc displacement without reduction. This might cause disturbances in mandibular movement and thus be called disc displacement without reduction with limited opening if the assisted opening is less than 40 mm (Schiffman et al. 2014).

4.2 Etiology

TMD has complex etiology and pathophysiology, thus the treatment may require multiprofessional cooperation. There are several risk factors that contribute to onset and persistence of TMD – they include physiological, psychological, environmental, and genetic factors (Maixner et al. 2011a, Fillingim et al. 2013). The physiological pain-related factors such as autonomic function and impaired pain regulation cause high state of pain

amplification, more intense response to potentially painful stimuli. It is highly emphasized that the physiological factors together with psychological factors contribute to TMD. Environmental factors that contribute to TMD include trauma and stress factors. Psychological factors, which are nowadays highly emphasized, comprise anxiety, negative mood, depression, stress, and somatization. The earlier-mentioned risk factors vary between individuals – they are influenced by genes, genetic expression, and receptor function. Also, several other factors such as female gender contribute to TMD. The factors associated with TMD can also be grouped as initiating, perpetuating and predisposing factors (McNeill 1983). Another way to explain the etiology is the biopsychosocial model of TMD that combines psychosocial, psychological, and physical point of view (Suvinen et al. 2005).

The physical or biomedical factors that contribute to TMD comprise altered or abnormal function and/or structure of the TMJs, muscles of mastication and occlusion but according to the multifactorial model, they are one component of the complex etiology of TMD (Suvinen et al. 2005). It has been suggested that there are different theories regarding TMJ including trauma and structural concepts such as anterior position or displacement of the articular disc. Abnormal muscle function such as muscle spasms are associated with TMD, but the association is bidirectional since muscle disorders can also be a consequence of TMD. Occlusal factors, such as occlusal interferences, as etiological factors of TMD are somewhat controversial – some studies have found a correlation between occlusion and TMD while some not.

Psychological factors have been widely recognized to be associated with chronic pain and TMD. According to Suvinen et al. (2005) psychological factors associated with TMD comprise emotional characteristics such as anxiety and how individuals experience their environment and adapt to it and its changes i.e., behavioral traits. Somatization is also an essential feature to take into account when assessing TMD. The prospective cohort OPPERA study found similar psychological predisposing risk factors that predict first-onset TMD – somatic symptoms, psychological symptoms, negative mood and stress in different concepts (Fillingim et al. 2013). Somatic symptoms refer to a person experiencing several physical symptoms and the association between somatic symptoms and TMD incidence are highly emphasized. It can be a result of behavioral causes, altered physiological function or CNS function. In conclusion, the biopsychosocial multidimensional model combines the physical and psychological factors with social environment and comprises pain as a concept, how

individuals perceive it and handle experienced pain which is important in optimal assessment and management of TMD.

4.3 Diagnostics

In 1992 The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) protocol with the dual-axis system was published to provide proper somatic diagnose based on the clinical findings (Axis I) and the contributing psychosocial factors as well as pain-related disability (Axis II) (Dworkin & Le Resche 1992). It was known that the RDC/TMD needed further investigation and update in the future to improve the Axis I diagnostic accuracy and Axis II clinical efficiency.

In 2014 the new Diagnostic Criteria for TMD (DC/TMD) protocol was published for both clinical and research use with an improved Axis I screening questionnaire, updated diagnostic criteria and taxonomic classification for TMD, and new Axis II instruments (Schiffman et al. 2014). DC/TMD comprise tools for general healthcare and for specialists to even more precise diagnostics. The aim is to provide personalized treatment for each patient. The new Axis I include diagnostic tools for four muscle-related somatic diagnoses – myalgia, local myalgia, myofascial pain, and myofascial pain with referral. Criteria for all the muscle-related disorders and arthralgia include history of pain in masticatory structures, and that the pain can be modified by jaw movement, function, or parafunction. The diagnostics for muscle-related disorders require patient's self-reported pain during jaw function located in the masticatory muscles based on the symptom questionnaire. Criteria for myalgia in the clinical examination include familiar pain felt during opening or muscle palpation confirmed by the examiner. Local myalgia requires that the pain is felt at the site of palpation, myofascial pain has additional spreading pain and myofascial pain with referral additional referred pain during palpation.

The TMJ-related diagnoses include arthralgia which refers to TMJ pain during movement and/or palpation, disc displacement with reduction, disc displacement with reduction with intermittent locking, disc displacement without reduction with limited opening and disc displacement without reduction without limited opening, degenerative joint disease, and subluxation. Additionally, there is headache attributed to TMD which means that all in all

the DC/TMD comprise 12 somatic diagnoses. Criteria for arthralgia in the symptom questionnaire require self-reported pain during jaw function, and in the clinical examination pain confirmed by the examiner in TMJ and familiar pain during palpation or jaw movement. Headache attributed to TMD requires either diagnosed myalgia or arthralgia and patient's self-reported headache during jaw function localized in temporal region based on the symptom questionnaire. The diagnostic criteria for TMJ disc displacement disorders are similarly based on self-reported symptoms and clinical signs in accordance with the diagnostic decision tree.

The new Axis II include five screening instruments: The Patient Health Questionnaire-4 (PHQ-4), The Graded Chronic Pain Scale (GCPS), pain drawing of the head, face and body, The Jaw Functional Limitation Scale (JFLS), and the Oral Behaviors Checklist (OBC). There are also comprehensive instruments for specialists for further assessment of psychosocial factors and comorbidities regarding treatment planning and prognosis since comorbidities and psychosocial factors can be associated with chronic pain. The International Network for Orofacial Pain and Related Disorders Methodology (INfORM), former International RDC/TMD Consortium Network, constantly improves the DC/TMD protocol (INfORM 2022).

5 CONNECTION OF AUTONOMIC FUNCTION WITH TMD

5.1 Altered brain activity in response to autonomic activation

There is emerging evidence that TMD patients show altered autonomic activity and ANS dysfunction. Vuong et al. (2020) investigated brain function with functional magnetic resonance imaging (fMRI) while the participants performed the Valsalva maneuver which is a breathing technique activating ANS (Vuong et al. 2020). The study sample consisted of 52 participants – 26 participants with both CFS and TMD (CFS+), 16 with CFS without TMD (CFS-) and 10 age-matched controls without the previous-mentioned or any other significant conditions. The fMRI revealed that during the Valsalva maneuver all three groups had increased activity in several brain regions. The significant finding was that there were two brain regions in the CFS+ group, the left insular cortex and left caudate, that stood out from the results with increased activity during autonomic challenge. The former was found in CFS+ compared to CFS- and the latter in CFS+ compared to controls. It is believed that pain related to TMD could intensify the insular activity since the insular cortex is one the brain regions associated with pain perception and modulation. It has been previously investigated that most CFS patients suffer from ANS dysfunction, and there is a higher degree of dysfunction in patients with CFS and TMD than CFS patients without the comorbid condition (Vuong et al. 2020, Robinson et al. 2015). However, the results can't be overlooked because of the fact that there were only 52 participants which is quite a small number to draw conclusions and the genders were unequally represented in each group (Vuong et al. 2020). The Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) or any clinical examination were not utilized in diagnosing TMD which is problematic. Also, these findings represent patients with CFS and TMD which means that the results can't be generalized solely on TMD.

5.2 Oxidative status

Few studies have been made to study the oxidative profiles and disease markers of bodily fluids in TMD patients (de Almeida & Amenábar 2016). There is evidence that the oxidative stress may play a role in TMD pathophysiology which makes it remarkable to study

regarding TMD etiology and management. Oxidative stress refers to a condition where the number of free radicals is increased, and the body can't eliminate the excessive radicals leading to a disturbance between the balance of the free radicals such as oxidants and the defending antioxidants. Free radicals are natural byproducts in a cell's metabolism and inflammatory processes can contribute to the production of free radicals and vice versa. de Almeida & Amenábar (2016) conducted a study investigating oxidative status of 60 participants half of which had TMD and pain while the other half had neither. Majority of the participants (54) were women. The study utilized the RDC/TMD questionnaire, clinical examination, and visual analogue scale (VAS). The total antioxidant capacity (TAC), the total oxidative status (TOS) and the oxidative stress index (OSI), the ratio between TOS and TAC, were determined from the participants' saliva. The statistically significant result was that the TMD group had reduced TAC and increased OSI values. In terms of TOS, the results were similar between the groups. In conclusion, the reduced TAC and increased OSI suggest imbalance in the oxidative status of TMD participants. It must be remembered that majority of the participants were women, and there was quite a large age distribution since the participants were aged between 10 and 60 years.

5.3 Dysfunction of the central nociceptive processing

There has been evidence for a long time supporting the assumption that the pathophysiologic mechanism behind TMD could originate from CNS since TMD patients suffer from widespread pain in other bodily sights in addition to TMJs and masticatory muscles, TMD subjects are more sensitive to painful stimuli and the signs and symptoms more prevalent in women than men (Sarlani & Greenspan 2005). It is suggested that the nociceptive neurons, which refers to sensory neurons that sense pain and noxious stimuli, have increased excitability in the CNS thus they transmit more action potentials in women than men which supports the fact that after repetitive stimuli the experienced pain is increased and the afterward sensations are more intense among women. TMD subjects have increased sensitivity to painful stimuli and women seem to have lower pain threshold and tolerance compared to males which support the assumption that central pain processing by electrically excitable nociceptors have altered function in women and in TMD cases compared to controls. A recent study by Knuutila et al. (2022), based on the Northern Finland Birth Cohort 1966 NFBC1966, investigated the association of pain sensitivity and TMD in 1,961

participants (Knuutila et al. 2022). 305 of the participants had at least one TMD subdiagnosis and 109 of them had multiple site pain. The participants were clinically examined by the DC/TMD protocol. Multiple site pain was self-reported through questions and pain measurements were examined with a device with increasing pressure to the skin of shoulder, shin, wrist and lower back. It was found that TMD subjects had increased sensitivity to painful stimuli and lower pain threshold and tolerance which support the assumption that central pain processing is altered in TMD cases compared to controls. There were notable differences between women and men – lower pressure pain tolerance in men was associated with multiple site pain related TMD whereas in women it was associated with myalgia and arthralgia. Women with the same TMD sub-diagnoses were also more susceptible to lower pressure pain threshold. The study had a large study population from NFBC1966, and the results were mostly line with previous studies. There are some limitations to the results and generalization since pain sites and self-reported pain after painful stimuli could be underestimated or exaggerated.

5.4 Sympathetic nervous system

Changes in pupil diameter reflect ANS function and it is also associated with HRV (Monaco et al. 2012). Therefore, pupillometry can be utilized when studying autonomic function. The light response causing the reduction in pupil size starts from the retina as optic nerve fibers carry the impulses to the pretectal nucleus (Barrett & Ganong 2012). From there they project to Edinger-Westphal nuclei and ultimately to the ciliary ganglion from which the postganglionic cholinergic fibers innervate the pupillary constrictor. Consequently, the contraction or miosis, that happens in light under cholinergic parasympathetic control is counterbalanced by beta-adrenergic innervation. The dilation or mydriasis, in turn, is controlled by adrenergic sympathetic branch from Budge's Cilio-Spinal Center innervating the dilator muscle and it is counterbalanced by the parasympathetic branch.

Monaco et al. (2012) examined pupil size of 20 female TMD patients and 20 female controls at rest position (RP) and at forced habitual occlusion (FHO) at two settings – infrared (darkness) and yellow-green light (light) (Monaco et al. 2012). Pupillometer recorded subjects at four episodes, and the results were compared to average pupil size. Within group compared pupil sizes, the paired t test revealed that in infrared conditions TMD patients had

smaller pupil sizes in FHO compared RP whereas controls had opposite findings in such conditions as expected. FHO was to represent the activation of sympathetic nervous system which induces pupil dilation. In addition, the FHO/RP ratio between the two groups was found to be higher in control group in infrared lightening and the light/darkness ratio was found to be significant between the groups at RP. These results support the assumption between dysfunction of ANS and TMD since TMD subjects had altered function of the pupils when exposed to stress – the pupil sizes decreased instead of the usual increase as with the controls. These findings demonstrate that TMD subjects tend to suffer from dysfunction in the sympathetic-adrenergic system. The study sample consisted of only 40 female participants which limits the generalization but still it supports previous studies regarding the topic.

5.5 The descending pain system

Transcutaneous electric nerve stimulation (TENS) is a pain-relieving method in treatment of TMD and has its effects in CNS pain signaling pathways (Monaco et al. 2015). 18 TMD cases and 18 controls participated in the study where they examined the effect of low-frequency TENS on pupil size through μ opioid receptors. Low-frequency TENS is thought to reduce pupil size through modulation of the descending pain signaling. Pupillometric recordings were done pre, during and post TENS stimulation after a certain time in infrared (darkness) and yellow-green (light) light. The study revealed that in yellow-green light TMD subjects had considerably smaller pupil sizes compared to controls already pre-TENS with a slight decrease in pupil sizes during TENS. However, after TENS stimulation, the pupil size reverted approximately to pre-TENS level. In the control group pupil size decreased even more post-TENS in the yellow green circumstances. Therefore, TMD subjects responded differently to low-frequency TENS stimulation without reduction in pupil size post-TENS. In infrared light pupil function was similar in both groups and during low-frequency TENS therapy the pupil sizes reduced as expected. Nevertheless, the results in TMD group didn't last as long as in the control group, similarly as with the yellow-green lightening. These results suggest dysfunction in the descending pain system in that reflected as altered pupil function in TMD subjects.

5.6 Cardiovascular factors

A large case-control study based on the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) cohort study, provided further evidence that ANS dysfunction is associated with TMD (Maixner et al. 2011b). The OPPERA baseline case-control study consisted of 3,263 participants – autonomic function of 185 TMD cases and 1,633 controls were examined in the current study. The RDC/TMD was used to classify TMD cases and controls. All participants' autonomic measures including arterial bloop pressure (BP), heart rate (HR), HRV and their different variables were assessed at rest and when exposed to orthostatic challenge and psychological Stroop Color-Word test and Stroop Pain-Affect tests that induce stress. Also, mechanical, and thermal pain sensitivity were assessed. The results highlighted that TMD cases stood out from controls in HRV, HR and baroreceptor sensitivity. It was found that reduced HRV in both time and frequency domains was associated with TMD cases at rest and when exposed to physical and psychological stressors. The stressors clearly provoked increased sympathetic activity and likewise, higher HR and reduced baroreceptor sensitivity was representative in TMD cases. Thus, the cardiac sympathetic tone is thought to be more prominent in TMD cases and these findings support this conception. Impaired baroreceptor sensitivity is characterized by lower LF measures and in this current study all HRV parameters, both time and frequency domains, showed a reduction among TMD cases. These results suggest dysfunction of ANS reflecting on heart function. Additionally, higher HR at rest has also found to be associated with higher risk of developing TMD together with increased pain sensitivity (Greenspan et al. 2013). A study by Eze-Nliam et al. (2011) utilized nocturnal polysomnography (PSG) to assess especially HRV (Eze-Nliam et al. 2011). The final study analysis included 37 TMD cases and 58 controls. Nocturnal HRV was found to be lower in TMD cases compared to controls which supports the other results.

A study by Chinthakanan et al. (2018) consisted of 21 TMD patients characterized by myofascial pain and 23 non-TMD controls and all participants were aged from 20- to 40-year-olds (Chinthakanan et al. 2018). The mean age in the TMD group was higher than in the control group and 19 of the TMD patients were females. TMD cases were included in the study based on long-term pain for over 3 months and RDC/TMD was used to make the clinical diagnosis. All participants' ECG was measured with a 24-hour Holter monitor to assess heart function, and the study also investigated pain sensitivity, anxiety and depression

and salivary cortisol level. The results supported previous studies – HRV was reduced in TMD cases based on lower time domain parameters, especially standard deviation of normal-to-normal intervals (SDNN) and standard deviation of the 5-minute average normal-to-normal intervals (SDANN).

5.7 Biopsychosocial aspects and ANS dysfunction

In the study by Chinthakanan et al. (2018), where the sample consisted of 21 TMD subjects and 23 healthy controls, the participants' pain intensity was assessed with visual analogue scale (VAS), psychological factors with adapted Hospital Anxiety and Depression Scales (HDAS) questionnaires, heart function with ECG and saliva was collected (Chinthakanan et al. 2018). Besides the results regarding HRV, it was highlighted that TMD patients suffered from greater psychological discomfort, pain intensity and higher cortisol concentration in saliva compared to controls. Since cortisol is considered a biomarker of stress, it is suggested that TMD patients might suffer from increased stress which results in altered autonomic function, but studies have opposite findings on this. It must be noted that when comparing all the factors with each other, no remarkable correlation was found.

Light et al. (2009) investigated stress hormone, cardiovascular and pain responses to different stressors with and without beta-blockade among 25 women with fibromyalgia syndrome (FMS), 29 with TMD and 34 healthy controls (Light et al. 2009). 11 of the 25 FMS subjects had comorbidity of TMD. A beta-blockade cluster was selected from the participants that consisted of 10 TMD and 10 FMS subjects and 16 healthy controls. In the beginning of the first rest period, the beta-blockade cluster participants were given either propranolol or placebo while other received nothing. Afterwards all participants' cardiovascular parameters and blood samples were taken. The stressors included postural standing, speech, and ischemic forearm pain to induce altered sympathetic activity, cardiovascular and stress hormone responses. The cardiovascular measures and blood samples were taken after each stressor along with pain ratings. The beta-blockade cluster conducted the same study about a week later with the other intravenous substance to the first one. The results after the tasks indicated that subjects with TMD and/or FMS have lower epinephrine and norepinephrine levels than healthy controls which reflect altered adrenergic function since the stress hormone levels should be higher in response to stressors. The

norepinephrine level also correlated inversely with pain severity. The beta-blockade propranolol aided in reducing adrenergic dysfunction and pain since the norepinephrine and epinephrine levels increased both in the TMD and FMS group. It must be noted that all the participants were women.

Jeong et al. (2021) investigated the association of autonomic dysfunction and TMD with a questionnaire survey that 71 TMD patients completed appropriately (Jeong et al. 2021). Diagnostics was based on to the RDC/TMD and autonomic dysfunction was assessed through the new Composite Autonomic Symptom Scale 31 (The COMPASS 31). The Brief Pain Inventory (BPI) questionnaire, Pain Catastrophizing Scale (PCS) and Symptom Checklist-90-Revised (SCL-90-R) were also utilized in the study. The study revealed that female gender, young age, depression, and pain interference correlated with higher COMPASS 31 scores. Orthostatic intolerance was found to be a significant finding in distinguishing female TMD patients from male patients and females were also generally more susceptible to ANS dysfunction. Against some of the results from previous studies, younger subjects were more susceptible to autonomic dysfunction in this current study. The results can't be overlooked since different-aged female participants were unequally represented and this most likely influenced the results. However, 29 male participants enrolled the study which gives insights into autonomic dysfunction in both genders. Even though there wasn't any control group in the study and autonomic function was assessed with a questionnaire this study reveals factors related to ANS dysfunction and provides interest for future studies.

6 DISCUSSION

This literature review suggests that TMD subjects have unusual function of the ANS which reflects as dysfunction of the sympathetic nervous system, reduced HRV along with other altered cardiovascular responses, dysfunction of the pain modulation and pain processing, altered brain activity in certain brain areas and changes in biopsychosocial aspects (Chinthakanan et al. 2018, Jeong et al. 2021, Knuutila et al. 2022, Maixner et al. 2011b, Monaco et al. 2012, Monaco et al. 2015, Light et al. 2009, Vuong et al. 2020). The role of ANS seems to be significant and several studies have results supporting each other. Above all, TMD is a frequent disorder affecting a large amount of people, and it has multiple dimensions regarding diagnostics, management, and treatment, thus TMD should be understood as a condition that may be linked with altered autonomic function. There are still quite a few studies assessing the connection of ANS and TMD and further qualitative and quantitative studies are needed to investigate autonomic function and TMD more closely. The study populations in majority of these studies were quite small and the genders were unequally represented which might affect the results. Any further conclusions can't be made about the causality of ANS dysfunction and first-onset TMD, but this is something to investigate further in the future.

Studies have brought new aspects to treatment of TMD. Treatment of TMD should be targeted for example to relieve of stress and increased sympathetic activity. Propranolol effects on altered epinephrine and norepinephrine levels and reduces total body pain which means that beta-blockers could be a treatment option in TMD (Light et al. 2009). One method to relieve stress and ANS dysfunction is applied relaxation which is suggested to be beneficial in treatment of TMD (Huhtela et al. 2020). Effectiveness of stabilization splint and applied relaxation was investigated with 96 Finnish students. Even though no major differences between the groups were found, applied relaxation was found to be more effective in relieving depressive symptoms compared to the splint group. The non-specific physical symptoms and general pain were also found to be substantially lower in the applied relaxation group which suggest that treatment of TMD benefits from newer treatment methods on top of the conventional methods. It must be noted that in the present study there were eventually only 40 participants left which is quite few considering the original number of participants. Still, it must be remembered that this is by far the only study to investigate

TMD treatment with applied relaxation and the results are primarily in line with previous studies.

In conclusion, there is convincing preliminary evidence that support the association between autonomic function and TMD. Several studies have found similar results regarding autonomic dysfunction and TMD that mostly support each other. However, majority of the studies have had small study samples with mostly women participants. There are also limitations to the results because case-control study designs do not provide information about the possible causal connection between the findings and TMD. In order to investigate the association more closely, longitudinal studies with coherent diagnostic protocols, larger study samples and both genders represented are needed. Long-term studies with larger cohorts are beneficial since incidence can be precisely investigated and the regular follow-ups enable to investigate the influence of autonomic risk factors on TMD. Also, clinical studies that focus on therapeutic management of autonomic dysfunction are needed both to identify the autonomic differences between cases and controls and it is essential in improving treatment of TMD.

REFERENCES

Ayouni I, Chebbi R, Hela Z & Dhidah M (2019). Comorbidity between fibromyalgia and temporomandibular disorders: a systematic review. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 128(1): 33-42.

Barrett K & Ganong W (2012). Ganong's review of medical physiology (24. international ed.). McGraw-Hill Medical, New York.

Basit H, Tariq MA, Siccardi MA. Anatomy, Head and Neck, Mastication Muscles. [Updated 2021 Jun 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-.

Chinthakanan S, Laosuwan K, Boonyawong P, Kumfu S, Chattipakorn N & Chattipakorn SC (2018). Reduced heart rate variability and increased saliva cortisol in patients with TMD. Archives of Oral Biology 90: 125-129.

Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: Review criteria, examinations and specifications, critique. Journal of Craniomandibular Disorders: Facial & Oral Pain. 1992;6:301–355.

de Almeida C & Amenábar JM (2016). Changes in the salivary oxidative status in individuals with temporomandibular disorders and pain. Journal of Oral Biology and Craniofacial Research 6: S1-S4.

Eze-Nliam CM, Quartana PJ, Quain AM & Smith MT (2011). Nocturnal heart rate variability is lower in temporomandibular disorder patients tvhan in healthy, pain-free individuals. Journal of Oral and Facial Pain and Headache 25(3): 232-239.

Fillingim RB, Ohrbach R, Greenspan JD, Knott C, Diatchenko L, Dubner R ym. (2013). Psychological factors associated with development of TMD: The OPPERA prospective cohort study. Journal of Pain 14(12 SUPPL.): T75-T90.

Greenspan JD, Slade GD, Bair E, Dubner R, Fillingim RB, Ohrbach R ym. (2013). Pain sensitivity and autonomic factors associated with development of TMD: The OPPERA prospective cohort study. Journal of Pain 14(12 SUPPL.): T63-T74.e6.

Huhtela, O. S., Koivisto, N., Hägg, V., & Sipilä, K. (2020). Effectiveness of applied relaxation method vs splint in treatment of temporomandibular disorders in Finnish students. Journal of oral rehabilitation, 47(2), 123–131.

International Network for Orofacial Pain and Related Disorders Methodology (INfORM) (2022). A Consortium Focused On Clinical Translation Research. https://ubwp.buffalo.edu/rdc-tmdinternational/ Accessed on 31.1.2022.

Jeong KH, Kim ME & Kim HK (2021). Temporomandibular disorders and autonomic dysfunction: Exploring the possible link between the two using a questionnaire survey. Cranio - Journal of Craniomandibular Practice.

Knuutila, J., Kivipuro, J., Näpänkangas, R., Auvinen, J., Pesonen, P., Karppinen, J., Paananen, M., Pirttiniemi, P., Raustia, A., & Sipilä, K. (2022). Association of temporomandibular disorders with pain sensitivity: A cohort study. European Journal of pain (London, England), 26(1), 143–153.

Light K, Bragdon E, Grewen K, Brownley K, Girdler S, & Maixner W (2009). Adrenergic dysregulation and pain with and without acute beta-blockade in women with fibromyalgia and temporomandibular disorder. The journal of pain, 10(5), 542–552.

Lövgren A, Häggman-Henrikson B, Visscher CM, Lobbezoo F, Marklund S & Wänman A (2016). Temporomandibular pain and jaw dysfunction at different ages covering the lifespan - A population based study. European Journal of Pain (United Kingdom) 20(4): 532-540.

Maixner W, Diatchenko L, Dubner R, Fillingim RB, Greenspan JD, Knott C ym. (2011a). Orofacial pain prospective evaluation and risk assessment study - The OPPERA study. Journal of Pain 12(11 SUPPL.): T4-T11.

Maixner W, Greenspan JD, Dubner R, Bair E, Mulkey F, Miller V ym. (2011b). Potential autonomic risk factors for chronic TMD: Descriptive data and empirically identified domains from the OPPERA case-control study. Journal of Pain 12(11 SUPPL.): T75-T91.

McNeill C. (1983). Craniomandibular (TMJ) disorders--the state of the art. Part II: accepted diagnostic and treatment modalities. The Journal of prosthetic dentistry, 49(3), 393–397.

Monaco A, Cattaneo R, Mesin L, Ciarrocchi I, Sgolastra F & Pietropaoli D (2012). Dysregulation of the Autonomous Nervous System in Patients with Temporomandibular Disorder: A Pupillometric Study. PLoS ONE 7(9).

Monaco A, Cattaneo R, Mesin L, Ortu E, Giannoni M & Pietropaoli D (2015). Dysregulation of the descending pain system in temporomandibular disorders revealed by low-frequency sensory transcutaneous electrical nerve stimulation: A pupillometric study. PLoS ONE 10(4).

Okeson JP (2019). Management of temporomandibular disorders and occlusion. 8 ED, St. Louis, Missouri: Elsevier.

Plesh O, Adams SH & Gansky SA (2011). Temporomandibular joint and muscle disorder-type pain and comorbid pains in a national US sample. Journal of Oral and Facial Pain and Headache 25(3): 190-198.

Purentaelimistön kipu ja toimintahäiriöt (TMD). Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim and the Finnish Dental Society Apollonia. Helsinki: The Finnish Medical Society Duodecim, 2021 (Accessed on 31.01.2022). Available online at: www.kaypahoito.fi

Robinson LJ, Durham J, MacLachlan LL & Newton JL (2015). Autonomic function in chronic fatigue syndrome with and without painful temporomandibular disorder. Fatigue: Biomedicine, Health and Behavior 3(4): 205-219.

Sarlani E & Greenspan JD (2005). Why look in the brain for answers to temporomandibular disorder pain? Cells Tissues Organs 180(1): 69-75.

Schiffman E, Ohrbach R, Truelove E ym. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group†. J Oral Facial Pain Headache 2014;28:6-27

Shaffer F & Ginsberg J. P. (2017). An Overview of Heart Rate Variability Metrics and Norms. Frontiers in public health, 5, 258.

Sipilä K, Suominen AL, Alanen P, Heliövaara M, Tiittanen P & Könönen M (2011). Association of clinical findings of temporomandibular disorders (TMD) with self-reported musculoskeletal pains. European Journal of Pain 15(10): 1061-1067.

Suvinen TI, Reade PC, Kemppainen P, Könönen M & Dworkin SF (2005). Review of aetiological concepts of temporomandibular pain disorders: Towards a biopsychosocial model for integration of physical disorder factors with psychological and psychosocial illness impact factors. European Journal of Pain 9(6): 613.

Vuong QC, Allison JR, Finkelmeyer A, Newton J & Durham J (2020). Brain Responses in CFS and TMD to Autonomic Challenges: An Exploratory fMRI Study. JDR Clinical and Translational Research 5(3): 224-232.