

Edouard Le Roux

**THE PHYSIOLOGY OF STRESS AND ITS ASSOCIATION WITH
TEMPOROMANDIBULAR DISORDERS: A NARRATIVE REVISION**

University Fernando Pessoa

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Fernando Pessoa, como parte dos requisitos
para a obtenção do grau de Mestre em
Medicina Dentária.

Edouard Le Roux

RESUMO

A etiologia da disfunção temporomandibular está envolta em alguma controvérsia, sendo atualmente resultado de um conjunto de fatores de risco. De entre um conjunto de fatores, etiologicos entre os quais: ambientais, traumáticos, comportamentais e psicológicos, o stress emocional tem sido indicado como preponderante no surgimento de tal condição em alguns pacientes. Do ponto de vista Fisiológico, o stress emocional é regulado pela atividade do eixo Hipotalâmico-Pituitária-Adrenocortical que por sua vez medeia a libertação de cortisol. A desregulação hormonal desencadeada por stress crónico está na genese de uma série de problemas metabólicos, resultantes do aumento da glicose no sangue.

Este trabalho tem como objetivo discutir a relação entre stress crónico, atividade do eixo hipotálamo-hipófise-adrenocortical e a disfunção temporomandibular, utilizando artigos que analisam os níveis de cortisol e de stress em grupos de pacientes com desordens temporomandibular. A literatura indica que o nível de cortisol é influenciado pela duração do estímulo stressante e que quanto mais tempo o indivíduo está exposto a esse estímulo, maior o risco de desregulação hormonal. De um total de 355 artigos encontrados através da PubMed que se relacionam com o tema, vinte e quatro artigos foram selecionados para leitura integral sendo apresentados oito estudos sobre a relação entre o estresse, o nível de cortisol e a disfunção temporomandibular. Foi encontrada uma correlação positiva entre estresse e disfunção temporomandibular em 6 estudos. Foi encontrada uma correlação positiva entre o nível de cortisol e disfunção temporomandibular em 3 estudos enquanto que 5 não encontraram associação.

Palavras-chave: “temporomandibular disorder”, “stress”, “cortisol”, “hypothalamic-pituitary-adrenocortical axis”.

ABSTRACT

The etiology of temporomandibular disorders is controversial and is currently the result of a set of risk factors. Among various factors, including environmental, traumatic, behavioral and psychological, emotional stress has been indicated as preponderant in the emergence of such condition in some patients. From a physiological point of view, emotional stress is regulated by the activity of the hypothalamic-pituitary-adrenocortical axis, which in turn mediates cortisol release. Hormonal dysregulation triggered by chronic stress is in the genesis of a number of metabolic problems resulting from increased blood glucose.

This paper aims to discuss the relationship between chronic stress, hypothalamus-pituitary-adrenocortical axis activity and temporomandibular dysfunction, using articles that analyze cortisol and stress levels in groups of patients with temporomandibular disorders. The literature indicates that the cortisol level is influenced by the duration of the stress stimulus and that the longer the individual is exposed to this stimulus, the higher the risk of hormonal dysregulation. From a total of 355 articles found through PubMed that relate to the topic, twenty-four articles were selected for full reading of which, eight studies were selected to discuss the relationship between stress, cortisol level and temporomandibular disorder. A positive correlation was found between stress and temporomandibular dysfunction in 6 studies. Also, a positive correlation was found between cortisol level and temporomandibular dysfunction in 3 studies while 5 found no association.

Keywords: “temporomandibular disorder”, “stress”, “cortisol”, “hypothalamic-pituitary-adrenocortical axis”

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ABBREVIATION LIST

TMD = Temporomandibular disorder

HPA = Hypothalamic-Pituitary-Adrenocortical

TMJ = Temporomandibular Joint

RDC/TDM = Research Diagnostic Criteria for Temporomandibular Disorder

DC/TMD = Diagnostic Criteria for Temporomandibular Disorder

CRH = Corticotrophin Releasing Hormone

ACTH = Adrenocorticotrophic Hormone

DHEA = dehydroepinendorsterone

OP = Orofacial Pain

HDAS = Hospital Depression and Anxiety Scale

PSS = Perceived Stress Scale

ANS = Autonomic Nervous System

BDI-II = Beck Depression Inventory II

I. INTRODUCTION

According to Laskin in 1969 “there are two aspects to the successful management of any disease process; one is the establishment of an accurate diagnosis; the other is an understanding of its etiology so that a rational treatment plan can be formulated. Unfortunately, in the management of many problems involving the temporomandibular joint, we have not been highly successful in either of these areas.” (Laskin, 1969)

The temporomandibular articulation plays an important role in mastication, jaw mobility and in verbal and emotional expression. Temporomandibular disorders (TMD) can affect the individual’s quality of life and his psychosocial functioning. It includes several disorders that can lead to chronic orofacial pain (Schiffman *et al.*, 2014; Ahmad and Schiffman, 2016; List and Jensen, 2017).

The etiology of TMD is considered multifactorial and those patients tend to exhibit a variety of psychosocial and behavioral characteristics such as chronic stress, depression and anxiety. Since the physiological response to stress is the activation of the hypothalamic-pituitary-adrenocortical (HPA) axis and because endogenous and exogenous stresses can influence cortisol rhythm, several studies suggest that the HPA axis activity is associated with TMD and could play a role in predisposing, precipitating, or prolonging TMD and TMD-pain (Lambert *et al.*, 2014; Salameh *et al.*, 2015; Jo *et al.*, 2016).

The objective of this bibliographic review is to investigate the relationship between TMD, stress and HPA axis activity.

1.1. Material and method

A bibliographic review was carried out using PubMed search engine, with the following keywords: “temporomandibular disorder”, “stress”, “cortisol”, “Hypothalamic-Pituitary-Adrenocortical axis,

The articles were selected according to their date of publication, a ten years inclusion were selected except one for its early definition of temporomandibular disorder and its research on the etiology. In this research a total 355 articles were found and 86 were selected after title and abstract reading. While 24 articles were used for full reading, 8 studies were discussed in detail.

II. DEVELOPMENT

2.1. TEMPOROMANDIBULAR DISORDERS (TMD)

2.1.1. DEFINITION AND EPIDEMIOLOGY

Temporomandibular disorder (TMD) is defined as a group of painful and/or dysfunctional conditions affecting the temporomandibular joints (TMJ), masticatory muscles and related structures. They are the most common cause of non-dental pain in the orofacial region (Natu *et al.*, 2018; Paulino *et al.*, 2018). TMD are a significant public health problem affecting 5% to 12% of the population and is the second most common musculoskeletal condition, after chronic low back pain, resulting in pain and disability. In adults the conditions affect more women than men with a ratio of 2:1 (Schiffman *et al.*, 2014).

In 2018, a study of more than three thousand patient – that evaluates the prevalence of TMD – concluded that this condition affects more adults between the age of 25 and 45. The study also showed that disk displacement with reduction is the most common disorder and that almost a third of them experience chronic pain (Talaat, Adel and Al Bayatti, 2018).

2.1.2. ETIOLOGY

The etiology of TMD is considered multifactorial, and several risk factors appear to predispose, precipitate, or prolong TMD and TMD-pain, including genetic and behavioral factors, macro or micro trauma, bio-psychosocial factors (stress, anxiety and depression) and biomechanical factors (occlusal factors, parafunctions such as bruxism and postural factors). (Chisnoiu *et al.*, 2015; List and Jensen, 2017; Paulino *et al.*, 2018)

Psychological factors such as stress, depression, anxiety and pain catastrophizing have been shown to be related to some headaches, muscle pain and muscle hyperactivity. There is considerable evidence that psychological factors are of great importance in the understanding of TMD (Chisnoiu *et al.*, 2015; List and Jensen, 2017).

2.1.3. SIGNS AND SYMPTOMS

The signs and symptoms associated with TMDs vary in their presentation and will often involve more than one component of the masticatory system. The three major signs and symptoms are pain in the TMJ region and palpation of the muscles of mastication, limited range of motion, and TMJ sounds (List and Jensen, 2017; Paulino *et al.*, 2018).

Chronic pain is the overwhelming reason for seeking TMD treatment. There are similarities with other chronic pain conditions such as chronic tension-type headache or migraine, low back pain and fibromyalgia, and cause much suffering for the individual. The pain in the TMJ region is aggravated by provocation, such as chewing, yawning, or talking (List and Jensen, 2017).

It has also been shown that most patient with chronic temporomandibular pain suffer from comorbidities such as fibromyalgia, headaches, back pain, otologic sings and muscles fatigue (Jasim *et al.*, 2014; Jo *et al.*, 2016; Paulino *et al.*, 2018)

2.1.4. TAXONOMY OF TMD

The Research Diagnostic Criteria for Temporomandibular Disorder (RDC/TMD), published in 1992, was constructed in order to help the diagnostic and research on temporomandibular disorder. It has been translated in more than 20 languages and is still used today. The RDC/TMD is made of a dual axis system: the Axis I and the Axis II. The Axis I concern the diagnostic somatic and/or biologic. The Axis II concerns the psychological state of the patient. However, it was determined that the RDC/TMD Axis I validity was below the target sensitivity of 0.70 and specificity of 0.95 and the scientific community ask for its revision (Peck *et al.*, 2014; Schiffman *et al.*, 2014; List and Jensen, 2017).

Later, in 2014, was created and published the Diagnostic Criteria for Temporomandibular Disorder (DC/TMD) dual Axis. Like the RDC/TDM, the DC/TMD have two domains : a physical Axis I (diagnosis) and a psychosocial Axis II (Schiffman *et al.*, 2014). The DC/TMD Axis I protocol includes its reliable and valid diagnostic criteria for common pain-related disorders and intra-articular disorders. It provides standardized evaluation of subjective symptoms, contains clearly defined examination methods, and utilizes specific diagnostic criteria to interpret the clinical findings (List and Jensen, 2017).

The DC/TMD Axis II assessment of the patient's psychosocial situation and pain consequences are based on validated instruments (questionnaires) and interpretation guidelines. It includes instruments for assessing pain behavior, jaw function, psychosocial functioning and distress (List and Jensen, 2017).

An expanded taxonomy has been created dividing the TMD into four groups: temporomandibular joint disorder, masticatory muscles disorder, headache attributed to TMD and associated structure (coronoid hyperplasia) (Peck *et al.*, 2014; Schiffman *et al.*, 2014).

2.2. NEUROPHYSIOLOGY OF STRESS

2.2.1. DEFINITION

Stress can be defined as a state of psychological or physiological strain caused by different stimuli that can be physical, mental or emotional; internal or external and tends to disturb the function of an organism and his homeostasis. Nowadays, emotional disturbances, daily schedule, competitive workloads, socioeconomic factors have led to increased stress levels in the modern lifestyle. (Salameh *et al.*, 2015)

2.2.2. TYPES OF STRESS

Through his research, Hans Selye defined in 1970 two type of stress. He termed the agreeable/beneficial and healthy response to a demand for adaptation as eustress and the disagreeable or pathogenic response as distress (Marcus and Baehrisch, 2013).

Later the neuro-endocrinologist McEwen, divide the concept of stress into "good stress", "tolerable stress" and "toxic stress" (McEwen *et al.*, 2015).

"Good stress" refers to the experience of rising to a challenge, taking a risk and feeling rewarded by an often positive outcome. A related term is "eustress".

"Tolerable stress" refers to situations in which bad things happen, but the individual with healthy brain architecture is able to cope. Here, "distress" refers to the uncomfortable feeling related to the nature of the stressor and the degree to which the individual feels a lack of ability to influence or control the stressor.

"Toxic stress" refers to the situation where bad things happen to an individual who has brain architecture that reflects effects of adverse early life events that have impaired the

development of good impulse control and judgment. Here, the degree and/or duration of “distress” may be greater. With toxic stress, the inability to cope is likely to have adverse effects on behavior and physiology, and this will result in a higher degree of allostatic overload (explained later in the paper) (McEwen, 2017).

2.2.3. MECHANISM OF STRESS

2.2.3.1. “FIGHT OR FLIGHT”

In first Walter Cannon describe in 1915 the “fight or flight” as the response of acute stress, or the response that occurs when an individual is facing a threat, linked to the activity of the adrenal gland releasing neurotransmitters from the sympathetic and central nervous systems. (Tan and Yip, 2018)

2.2.3.2. GENERAL ADAPTATION SYNDROME

Hans Selye distinguished acute stress from chronic stress, terming the latter condition “general adaptation syndrome”, also known as Selye’s Syndrome. The General Adaptation Syndrome divides the chronic stress response into three phases: the alarm reaction, the stage of resistance and the stage of exhaustion. When individuals are exposed to a stressor, they are at first caught off-guard, and then he adapts to maintain homeostasis until he eventually fall to exhaustion, which can lead to depression or anxiety. Threw experimentation on rats, Hans Selye cleverly linked the hypothalamic-pituitary-adrenal axis to the way the body respond to chronic stress (Buckner *et al.*, 2017; Natu *et al.*, 2018; Tan and Yip, 2018).

2.2.3.3. CONCEPT OF ALLOSTASIS, ALLOSTATIC LOAD AND OVERLOAD (Figure 1)

Finally McEwan described the concept of allostasis and allostatic load and overload. In a changing social and physical environment, the brain and body respond physiologically and behaviorally in order to adapt (McEwen, 2017).

Physiologically, the response is composed by the sympathetic and parasympathetic systems, the hypothalamic–pituitary–adrenal (HPA) axis, the immune system and the metabolic hormones process within all organs, including the brain. It operates non-linearly and promote adaptation via “allostasis” (active process of adaptation and maintaining homeostasis). But the same mediators have biphasic effects and can also promote pathophysiology when

overused or when their activity is out of balance with each other. This is the allostatic load or overload.

Allostatic load refers to the cumulative effect of multiple stressors as well as the dysregulation of the nonlinear network of allostasis (for example, production of cortisol, adrenalin or inflammation in response to a challenge).

Allostatic overload refers to the cumulative pathophysiology that can result from this dysregulation and excessive stress.

Allostasis, allostatic load and overload, are more precise biological concepts than 'stress' to describe adaptation and mal-adaptation to 'stressors'. They include the physiological effects of health-promoting and health-damaging behaviors as well as stressful experiences. Health behaviors – such as smoking, alcohol, lack of sleep – resulting from the experience of stress, also have a role and contribute to allostatic load and overload (McEwen *et al.*, 2015).

2.2.4. THE PHYSIOLOGY OF STRESS

The brain determines what is threatening, stores memories, and regulates the physiological as well as behavioral responses to stressors that may be damaging or protective. Thereby the brain is the central organ of stress and adaptation to social and physical stressors

The physiological responses that produce adaptation through 'allostasis' include not only the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system, but also their nonlinear interactions with the metabolic system and the pro- and anti-inflammatory components of the immune defense system (McEwen *et al.*, 2015).

2.2.4.1. SYMPATHETIC AND PARASYMPATHETIC SYSTEM

Neurologically, humans function on a continuum between sympathetic (fight or flight) and parasympathetic (rest and digest). The sympathetic nervous system promotes catabolic tissue breakdown and fat metabolism to mobilize glucose for energy. At the other end, the parasympathetic nervous system promotes healing, repair, immunity, and the anabolic growth required for restored energy reserves and longevity. This delicate balance between sympathetic and parasympathetic activity is critical for long-term physical and psychological health. (Hannibal and Bishop, 2014)

2.2.4.2.THE ACUTE STRESS RESPONSE

In the initial stage of the acute stress response, the amygdala signals to the brain to release sympathetic adrenergic catecholamine, norepinephrine and epinephrine. Once released into the blood flow, catecholamine neurotransmitters increase heart rate, blood pressure, and respiration, vasoconstrict arterioles and stimulate sweat secretion and pupillary dilation (Hannibal and Bishop, 2014).

Approximately 15 minutes after the onset of stress, a neuroendocrine response follows. The amygdala activates the HPA axis (Figure 2) by signaling the hypothalamus to release corticotrophin releasing hormone (CRH). Then, this hormone triggers the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, and ACTH stimulates the release of cortisol and cortisone from the adrenal cortex. Increased levels of cortisol mobilize glucose and tissue substrates for fuel, suppress non vital organ systems, and decrease inflammation (effect anti-inflammatory) to allow further effective management of stress (Hannibal and Bishop, 2014; Staniszewski *et al.*, 2018).

2.3. THE RELATIONSHIP BETWEEN STRESS, HPA AXIS ACTIVITY AND TMD

The relationship between stress and temporomandibular disorders:

The etiologies of temporomandibular disorders are considered as a heterogeneous group of psychophysiological disorders. More precisely, psychological stress – such as depression, anxiety and stress – are considered as a risk factor. However, the prevalence and role of psychological factor might vary depending on the pain status of the patient and the longer the pain persist (Jasim *et al.*, 2014; Kobayashi *et al.*, 2017). Several studies in the last decades aim to investigate the relationship between psychological stress and TMD. Past studies revealed the possible predisposing, triggering and/or worsening role of some psychological factor. Plus, they revealed a high comorbidity with TMD and other pain condition such as muscle tension, which may result from a poorly adapted response to psychological stress (Tosato *et al.*, 2015; Kobayashi *et al.*, 2017).

The relationship between chronic stress and HPA axis activity:

Hypothetically, the response produced by chronic stress is associated with an increased activity of the HPA axis. Repeated exposure to stressful situations can trigger over activation of the HPA axis increasing the cortisol levels. High cortisol levels can be detrimental to the organisms health and may provide a link between mental stress and physical illness (Salameh *et al.*, 2015; Kobayashi *et al.*, 2017).

However, there might be two subgroups of patients: one that responds with an increase in cortisol release in response to chronic stress (over activation) and another that show a dysfunctional cortisol response (decrease in cortisol release). In fact, it is hypothesized that chronic reactivation of stress response exhausts the HPA axis, and cortisol dysfunction seems to be implicated in pain and inflammation (Hannibal and Bishop, 2014; Jasim *et al.*, 2014).

Pain as a cause or consequence of stress

Long-term stress has been shown to attenuate the cortisol awakening response and contribute to morning fatigue, pain, and inflammation. In the other hand acute pain is a stressful stimulus that is likely to elicit cortisol secretion. Acute pain is associated with a pathological process serving a biological purpose of warning and protecting the organism. Yet, chronic pain has lost this warning and protective function and may be flowed by

increasing underlying biological and psychological process (Hannibal and Bishop, 2014; Jasim *et al.*, 2014).

The relationship between TMD and HPA axis activity:

Since TMD is a somatic manifestation of stress, and given the higher stress levels in patients with TMD compared to healthy subject, it is reasonable to expect that the end product of the HPA axis in patients with TMD may be different from those in healthy condition (Salameh *et al.*, 2015; Jo *et al.*, 2016).

III. DISCUSSION

After research, eight studies were selected for their investigation on cortisol levels in patients with TMD (data in table 1). A 5 years inclusion were used in order to select articles using the DC/TMD classification, but none of the articles found were using the last taxonomy published in 2014. Moreover, only studies investigating all TMD cases in general were selected. Some studies investigating only specific TMD cases were excluded.

In the case-control study from Lambert *et al.* hair cortisol concentration was measured in patients with TMD. They investigated the relationship between TMD and stress, TMD and hair cortisol levels, and, stress and hair cortisol levels. Despite higher perceived stress in TMD patients, these same patients had lower levels of cortisol in hair samples. This study found a weak and negative relationship between perceived stress and hair cortisol levels (Lambert *et al.*, 2014)

The cross-sectional study from Tosato *et al.* investigated the correlation of salivary cortisol levels with the activities of the masseter and anterior temporal muscles in women with TMD using electromyography (EMG). They use the Fonseca Patient History Index to diagnose the severity of TMD, thus patient are classified in absence, mild, moderate and severe TMD. Muscle activity was evaluated during non-habitual chewing (isotonic contraction), maximum voluntary clenching (isometric contraction), and with the mandible in the physiologic rest position. They found a strong correlation between salivary cortisol and EMG activities among women with severe TMD. Also, a positive and strong correlation between cortisol and TMD severity was found. According to the authors, muscle activity was greater among individuals with severe temporomandibular disorder. Positive correlations were found among electromyographic activity, salivary cortisol and the degree of temporomandibular disorder severity (Tosato *et al.*, 2015).

Chinthakanan *et al.* aimed to compare pain intensity, heart rate variability (in order to measure the autonomic nervous system activity), psychological factors, and salivary cortisol level between TMD patients and a control group. Based on the RDC/TMD they use the Visual Analog Scale for pain intensity, the HDAS for depression and anxiety, and salivary cortisol. Pain intensity, psychological stress and cortisol level were higher in TMD group and showed a positive correlation. HRV parameters were lower in the TMD group. According to the

authors TMD patients may benefit from interventions that can restore ANS function and stress balance (Chinthakanan *et al.*, 2018).

The cross-sectional study from Staniszewski *et al.* aim to assess if the HPA axis is upregulated in TMD patients. They measure salivary cortisol and salivary cortisone in 44 TMD cases and 44 controls. They use the HDAS and 2 items from the Coping Strategies Questionnaire in order to measure depression, anxiety and catastrophizing. They found higher cortisol levels and cortisone levels in TMD cases, as well as higher score of anxiety, depression and catastrophizing. These results indicated a possible upregulation of the HPA axis in TMD cases (Staniszewski *et al.*, 2018).

Kobayashi *et al.* aim to measure salivary cortisol levels, salivary alpha-amylase and anxiety symptom (with the MASC-Brazilian version) in children between 7 and 14 years old. No significant differences were observed in cortisol levels and alpha-amylase levels between TMD cases and control. Despite high score of anxiety in children with TMD, there is no significant correlation between the anxiety and cortisol (Kobayashi *et al.*, 2017).

Jasim *et al.* aim to compare the salivary cortisol levels, pain intensity and psychological factors between patients with chronic and acute orofacial pain (OP) and pain-free subjects. They use a numeric rating scale for pain intensity and the PSS for perceived stress as well as the Symptom Checklist 90 for depression and somatisation. Patients with chronic OP showed higher score in depression, somatisation and perceived stress, but no differences were observed in cortisol levels between the three groups. According to the authors no statistical correlation was found between perceived stress, depression and somatisation score and cortisol levels (Jasim *et al.*, 2014).

The study from Salameh *et al.* aim to measure salivary cortisol levels, perceived stress with the PSS and depression/distress and somatisation with the RDC/TMD Axis II questionnaire. No statistically significant difference between the TMD groups at cortisol concentration despite higher stress levels, higher score in depression and somatisation and differences in cortisol levels among patient with chronic OP (Salameh *et al.*, 2015).

The study from Jo *et al.* aim to investigate the function of the HPA axis in relation to variables of the RDC/TMD Axis II and comorbid depression in women with TMD. They use the RDC/TMD Axis II for pain intensity, the Beck Depression Inventory (BDI)-II and measure salivary cortisol and salivary dehydroepinendorsterone (DHEA) (produced in

response to ACTH). There were no significant differences in the levels of diurnal cortisol and DHEA secretion between groups. But the ratio of cortisol secretion after awaking/DHEA secretion after the awaking period was significantly associated with pain and depression (Jo *et al.*, 2016).

Limits in the cortisol sample collection:

There are three ways to measure cortisol levels: salivary, plasmatic, capillary. The quantification of salivary cortisol seems to be a reliable index of free cortisol in the plasma (Jasim *et al.*, 2014; Tosato *et al.*, 2015). However, the time of the day exerts and influences on the concentration of the hormone (figure 3). Cortisol secretion possess a diurnal rhythm: there is a robust increase in cortisol levels during the first hour after waking called the cortisol awakening response. This increase is followed by a decline over the rest of the day. Such variation means that exact timing of collection is critical if cortisol concentrations are to be meaningfully compared (Lambert *et al.*, 2014; Tosato *et al.*, 2015; Jo *et al.*, 2016)

Saliva samples were taken for all the study in the morning, but have a strong variation during the first hour after awaking. For example in the study from Staniszewski *et al.* all subjects in the control group collected saliva 2 hours and 45min after awakening (Staniszewski *et al.*, 2018). In another study saliva samples were taken between 7:45AM and 12:15AM. The patients who have their saliva samples taken before 10:00 AM showed greater variations in salivary cortisol than the patients who have their samples taken at 10:00 AM and after-wards (Jasim *et al.*, 2014). This allow us to think that variation of cortisol levels in the first hours, and variation in the samples collection after each individual awaking is likely to affect the statistical analysis.

Conclusions and theories:

On these eight studies two found a statistically significant strong relationship between high cortisol levels and TMD (Tosato *et al.*, 2015; Staniszewski *et al.*, 2018), one found a statistically significant positive relationship (Chinthakanan *et al.*, 2018) and the five others found no significant relation between TMD and cortisol levels. These differences in results between studies may be due to differences in study design, population and socioeconomic factors (Salameh *et al.*, 2015).

The study from Kobayashi *et al.* suggests that TMD may involve dysregulation of sympathetic activity by investigating level of salivary alpha-amylase (digestive and antimicrobial enzyme). The salivary alpha-amylase increases in stressful conditions and induces catecholamine production (first response to stress), reflecting the sympathetic activity. But they found no significant differences between groups (Kobayashi et al., 2017).

The study from Lambert *et al.* found lower hair cortisol in patient with higher stress score. When comparing with other results they suggest a possible mechanism: chronic stress elicits both an increased and a decreased production in cortisol, at different stages following onset of stress (Lambert *et al.*, 2014)

The study investigation HRV parameters found with their results a possible dysregulation of the ANS, itself composed by the sympathetic system that control the HPA axis activity and cortisol levels (Chinthakanan *et al.*, 2018).

Moreover, the results of the study that measure cortisol and DHEA show dissociation in cortisol and DHEA secretion. These two hormones are normally related to ACTH secretion. Thus the study suggests a dysfunction in the HPA axis activity in patient with TMD-pain and depression despite no differences in cortisol secretion in the TMD group and the control group (Jo *et al.*, 2016).

Yet, three study found no differences and no association with cortisol levels (Jasim *et al.*, 2014; Salameh *et al.*, 2015; Jo *et al.*, 2016) despite higher stress/depression/anxiety score. Jasim et al. suggest that this does not exclude the possibility of a dysregulation in the HPA axis among patients with chronic OP (Jasim et al., 2014). In fact Lambert et al. cite another study suggesting that overtime, HPA axis activity subsides and cortisol secretion rebounds to below normal levels. This is consistent with the theory – from Selye – of the General Adaptation Syndrome with the concept of allostatic load. When overuse the system designed to manage stress leads to impairment of the HPA function including a decrease in responsiveness stress and disturbance in the secretion of cortisol or other mediator (Lambert *et al.*, 2014)

It seems that psychosocial stress plays an important role in etiopathogenesis of TMD (Salameh *et al.*, 2015). On the eight studies, six investigate the association between TMD and psychological factors (such as stress, depression and anxiety) by measuring them. They all found higher levels of stress and/or depression and/or anxiety in TMD cases compared to

controls. Moreover, Jasim et al. explained that the PSS score was positively related to the depression and somatisation levels.

All studies agree on one point: Psychological stress and depression constitute risk factors for TMD and an increase in stress occurred in the TMD group. Stress may be essential in the triggering and maintenance of the musculoskeletal disorders such as TMD. However, the role of stress in the etiology of TMD remains unclear and each risk factor needs to be considered to appropriately diagnose and plan the management strategies (Jasim *et al.*, 2014; Tosato *et al.*, 2015; Kobayashi *et al.*, 2017; Chinthakanan *et al.*, 2018; Staniszewski *et al.*, 2018).

IV. CONCLUSION

The study of temporomandibular disorder seems to be halfway of its complete understanding. The multifactorial etiology of temporomandibular disorders and the comorbidity with other diseases, complicates the understanding and proper treatment.

Nowadays, the mechanism and the physiology of acute stress seem to be understood. While chronic stress is considered today as one of the main diseases that impact our daily life, its physiological response seems to be misunderstood. Nevertheless, the literature suggests that the physiological response to chronic stress consists of a dysfunction in secretion of cortisol and a dysregulation of the HPA axis activity.

Many studies confirm the association between stress and TMD. Psychosocial factors are considered as one of the factors that can predispose and trigger TMD. Also the literature aim to investigate and tend to confirm that stress has an impact and is associated with the HPA axis activity. This let us hypothesize that in chronic stress the first response is a higher cortisol release, followed by a cortisol rebound to normal, and then in a lower cortisol release. This hypothesis could refer to the concept of allostatic load and overload.

While some studies did not found any significant association between TMD and HPA axis activities, the difficulty to measure how long chronic stress have impacted the patient and the severity of it, complicates the possibilities to affirm the previous hypothesis. Thus, it could be a new path for futures studies, to find a way to measure stress and evaluate in witch stage of the general adaptation syndrome the patient is.

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VI. ANNEXE

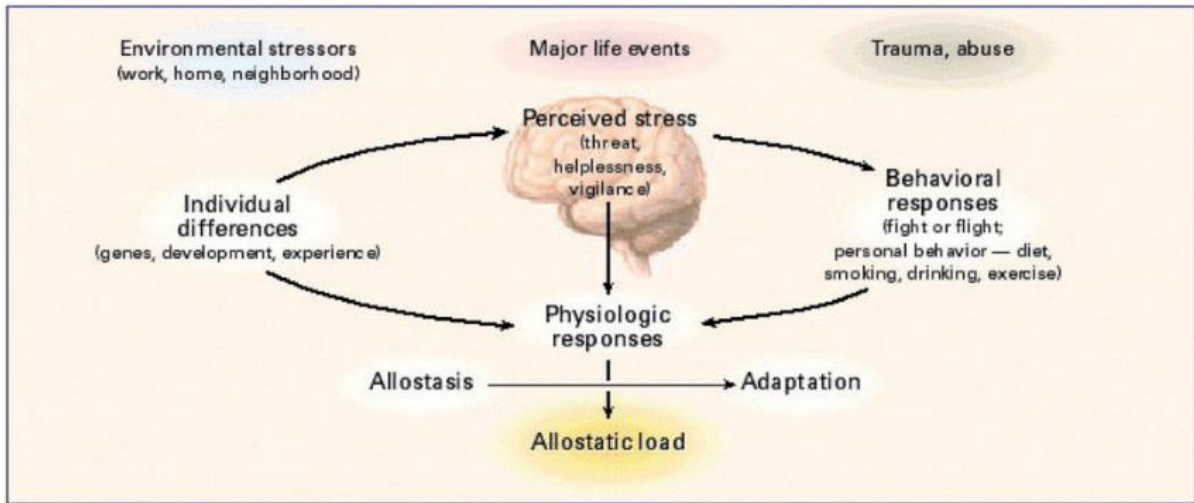


Figure 1 – Central role of the brain in allostasis and the behavioral and physiological response to stressors (McEwen, 2017)

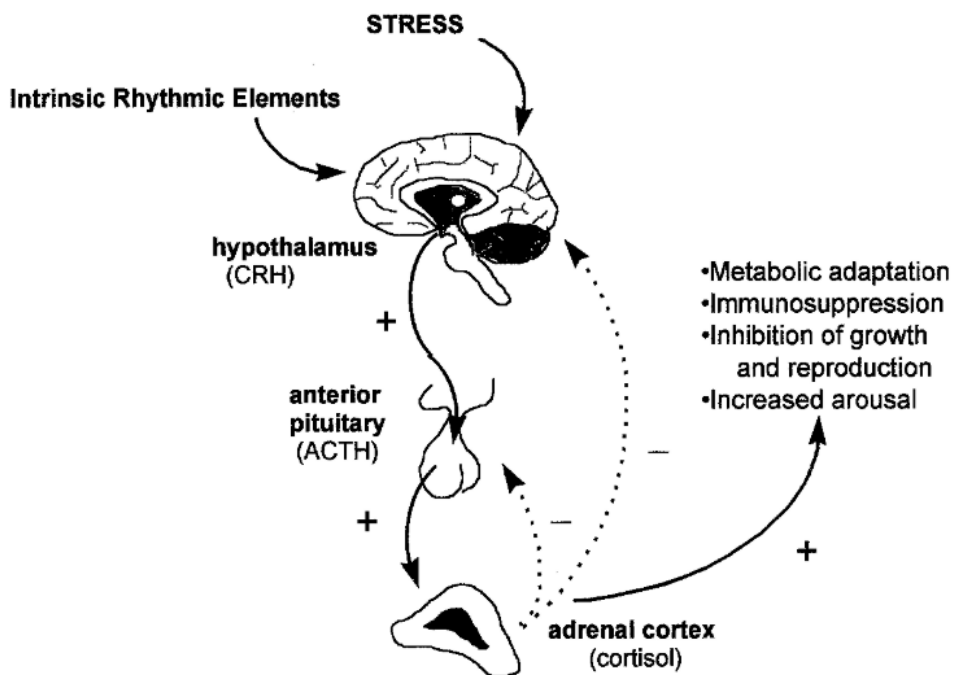


Figure 2 – HPA Axis (Korszun *et al.*, 1998)

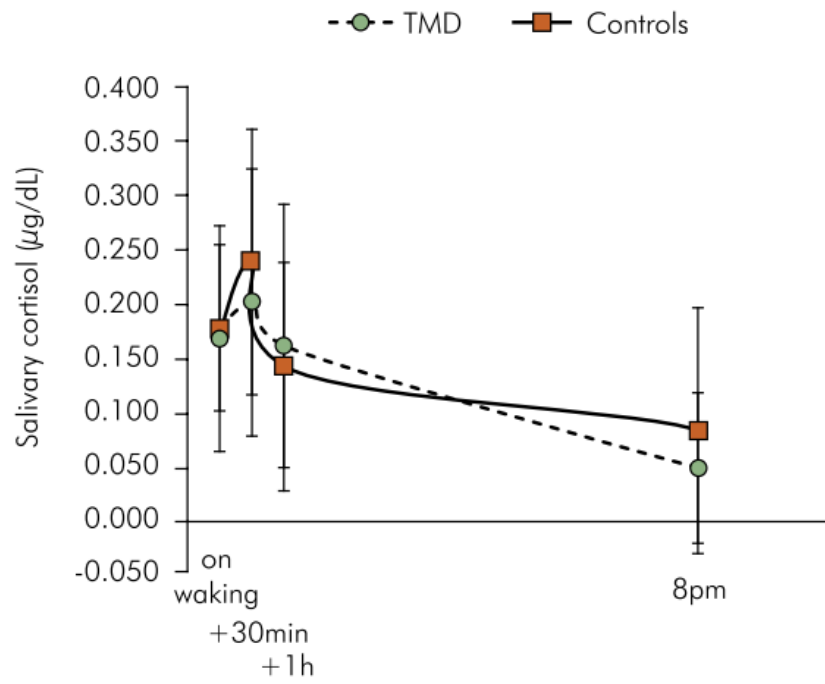


Figure 3 - Salivary cortisol profiles in TMD and control groups. (Kobayashi *et al.*, 2017)

Table 1 – Data extraction : aim, method and results

TITLES AND REFERENCES	AIM	METHOD	RESULTS AND CONCLUSION
The relationship between temporomandibular disorders and stress-associated syndromes. (Lambert <i>et al.</i> , 2014)	To clarify the role of stress in TMD	Hair cortisol PSS - 14	TMD cases perceived higher stress than controls. Hair cortisol concentration was lower in TMD cases than controls. Weak negative relationship between perceived stress and hair cortisol concentration.
Correlation of stress and muscles activity of patients with different degrees of temporomandibular disorder. (Tosato <i>et al.</i> , 2015).	To investigate the correlation of salivary cortisol levels with the activities of the masseter and anterior temporal muscles of patients with different degrees of TMD	Salivary cortisol Electromyography (EMG)	Muscle activity was greater among individuals with severe TMD Positive correlations were found among electromyographic activity, salivary cortisol and the degree of TMD severity.
Reduced heart rate variability and increased saliva cortisol in patients with TMD (Chinthakanan <i>et al.</i> , 2018)	To compare pain intensity, HRV, psychological factors, and salivary cortisol level between TMD patients and a control group	Salivary cortisol VAS for pain intensity. Hospital Anxiety and Depression Scales (HADS). Holter monitor for HRV (Heart Rate Variability) in order to measure the autonomic nervous system (ANS) activity.	TMD cases had greater pain intensity and psychological distress Pain intensity showed a positive correlation with psychological distress. Lower HRV parameters in the TMD group Pain intensity was negatively associated with HRV. Higher salivary cortisol levels in the TMD group TMD patients may benefit from interventions that can restore ANS function and stress balance.
Temporomandibular disorders related to stress and HPA-Axis regulation. (Staniszewski <i>et al.</i> , 2018)	To assess if the hypothalamic-pituitary-adrenal (HPA) axis is upregulated in TMD patients	Salivary cortisol Salivary cortisone Hospital Anxiety and Depression Scale (HADS) 2-item version of the Coping Strategies Questionnaire regarding catastrophizing.	Higher cortisol levels Higher cortisone levels Higher cortisol/cortisone ration Higher Anxiety/depression and catastrophizing scores
Salivary stress biomarkers and anxiety symptoms in children with and without temporomandibular disorders. (Kobayashi <i>et al.</i> , 2017)	To evaluate the salivary alpha-amylase (sAA), cortisol levels, and anxiety symptoms in children with and without TMD	Salivary cortisol Salivary Alpha-Amylase Multidimensional Anxiety Scale for Children (MASC-Brazilian version)	No significant differences in the salivary cortisol Higher score in anxiety and MASC total score, No significant correlation between the MASC total score, cortisol, and sAA levels.

<p>Salivary cortisol and psychological factors in women with chronic and acute oro-facial pain. (Jasim <i>et al.</i>, 2014)</p>	<p>To compare the salivary cortisol level, pain intensity and psychological factors between patients with chronic and acute oro-facial pain (OP) and pain-free subject</p>	<p>Salivary cortisol Numeric rating scale for pain intensity Symptom Checklist 90-revised for depression and somatisation PSS</p>	<p>No significant group differences. In cortisol levels Patients with chronic OP showed significantly higher scores for depression, somatisation and perceived stress</p>
<p>Investigation of the relationship between psychological stress and temporomandibular disorder in adults by measuring salivary cortisol concentration: a case-control study. (Salameh <i>et al.</i>, 2015)</p>	<p>To assess any differences in salivary cortisol concentration, scores of PSS, and scores of depression and distress between TMD patients and matched controls.”</p>	<p>Salivary cortisol PSS – 10 Psychosocial measure of RDC/TDM axis II</p>	<p>Temporomandibular disorder cases perceived higher stress than controls and higher levels of depression and distress. Significant differences in salivary cortisol concentration have been observed between TMD cases and controls Increased occurrence of this disorder in women has been observed. There was no statistically significant difference between the TMD groups at cortisol concentration (muscle disorders, disc displacement, arthralgia/arthrosis/ arthritis)</p>
<p>Association of pain intensity, pain-related disability, and depression with hypothalamus-pituitary-adrenal axis function in female patients with chronic temporomandibular disorders. (Jo <i>et al.</i>, 2016)</p>	<p>To explore the function of the hypothalamus–pituitary–adrenal (HPA) axis and depression score in TMD patient</p>	<p>Salivary cortisol Salivary DHEA (dehydroepiandrosterone) Beck Depression Inventory (BDI)-II</p>	<p>no significant differences in the levels and diurnal patterns of cortisol and DHEA secretion Ratio of cortisol/DHEA post-waking period was significantly associated with pain and depression Pain intensity and pain-related disability scores were also significantly associated with BDI-II total scores.</p>