The journal of
PROSTHETIC AND IMPLANT DENTISTRY
Official Publication of Indian Prosthodontic Society
Kerala State Branch

POTENTIAL BIOMARKERS IN TEMPOROMANDIBULAR DISORDERS: CURRENT INSIGHTS AND FUTURE PROSPECTS

*Pavithra B, ** Vivek V Nair, ***Harshakumar K , ** Prasanth Viswambharan

* Postgraduate Student, ** Professor, ***Vice Principal, Professor, Head of the Department, Department of Prosthodontics and Crown & Bridge, Govt. Dental College, Thiruvananthapuram. Corresponding author: Dr Pavithra B Email: pavithraboobalan97@gmail.com

https://doi.org/10.55231/jpid.2025.v08.i02.03

Abstract

Temporomandibular disorders (TMD) are prevalent conditions affecting the temporomandibular joint (TMJ), masticatory muscles, and surrounding areas, leading to pain and functional impairment. Diagnosing and managing TMD is complex due to its multifactorial etiology involving biological, psychological, and sociocultural factors. Biomarkers have emerged as promising tools for precise diagnosis and monitoring of TMD. This review explores various biomarkers, including inflammatory markers like IL-1, IL-6, and TNF-α, salivary markers such as oxidative stress indicators and salivary cortisol, and degradative enzymes like MMPs and ADAMTS. Neurotransmitters (e.g., glutamate, serotonin) and growth factors (e.g., NGF, VEGF) are also highlighted for their roles in TMD pathophysiology. Additionally, bone and neuroimaging biomarkers offer insights into structural and functional changes in the TMJ and brain, enhancing diagnostic accuracy. Emerging biomarkers like collagen markers, hormones, and lubricin are discussed for their potential in clinical diagnosis and treatment. Despite their promising role, challenges remain in biomarkers' standardization, specificity, and validation. Future research should focus on advanced proteomics, non-invasive sampling methods, and large-scale studies to confirm the clinical utility of biomarkers in TMD management, paving the way for personalized oral health care.

Keywords: Temporomandibular disorders, Biomarkers, TMJ, TMD, diagnostic markers

Introduction

Temporomandibular disorder (TMD) is a prevalent musculoskeletal condition affecting the temporomandibular joint (TMJ), masticatory muscles, and the periauricular region, characterized by persistent pain and functional impairment. It is recognized as the most common form of non-odontogenic orofacial pain, with patients often experiencing restricted or asymmetrical mandibular movements, alongside audible joint sounds such as clicking, popping, grinding, or crepitus. TMD symptoms extend to

the ears, eyes, throat, and head, with headaches frequently reported in frontal, temporal, parietal, occipital, and neck regions. Early studies found that 1–75% of the population show at least one noticeable sign of TMD, while 5–33% experience subjective symptoms.[1] Globally, an estimated 10% of the general populace is affected by TMD, with the prevalence reaching around 34%, showing a notable female predominance in an age range from 20 to 40 years. In the Indian population, prevalence ranges from 17% to over 50%, indicating significant variability.[2] The etiology and pathophysiology of TMDs are complex and multifactorial, involving biological, psychological, and sociocultural determinants. Due to the large portion of the population experiencing painful TMD, it's crucial to develop new and precise diagnostic methods to enhance the current standard of care. Diagnosing TMJ-related problems is exceedingly difficult, and there is ongoing debate regarding the appropriate treatment. Furthermore, the variation in TMD findings among individuals over time significantly adds to the complexity of TMD diagnosis and treatment.

The connection between TMD and an increased level of biochemical markers being acknowledged permits the exploration of more precise and groundbreaking diagnostic biomarkers within this area. According to the FDA, biomarkers are "a defined characteristic that is objectively measured as an indicator of normal biological process, pathologic process or biological responses to a therapeutic intervention".[3] One condition that possess a significant global health problem is temporomandibular disorder (TMD These biomarkers can significantly assess the extent and activity of the deterioration in cartilage and bone for diagnostic and prognostic determinations. Identifying a biomarker will supply a measurable indication for diagnosing TMD in its early stages and will assist in monitoring the treatment process. The acquisition of biomarkers for temporomandibular joint (TMJ) disorders involves a diverse array of techniques spanning molecular, imaging, and clinical methodologies. Molecular biomarkers are typically obtained through minimally invasive procedures: synovial fluid is collected via arthrocentesis, saliva is gathered through passive drool or salivette collection, and blood samples are drawn for serum or plasma analysis. This review is intended to offer a summary of the latest research on TMJ biomarkers, examining their possible uses in clinical settings and identifying areas that require further study.

Discussion:

INFLAMMATORY MARKERS:

Pro-inflammatory cytokines play a crucial role in both acute and chronic inflammation. They can significantly stimulate bone resorption while inhibiting bone formation, with elevated levels being linked to inflammatory diseases. These molecules form complex immunological networks that include pro-inflammatory cytokines like interleukin 1 (IL-1), IL-6, and TNF, as well as anti-inflammatory mediators such as IL-10 and transforming growth factor-beta (TGF-β).[4] Despite some conflicting findings regarding cytokines, high levels of pro-inflammatory cytokines are generally associated with symptoms of temporomandibular disorders (TMDs), including osteoarthritis (OA) and internal derangement (ID). These mediators contribute to the degradation of cartilage and bone joints by releasing proteinases and other inflammatory molecules.

IL-1:

IL-1 comprises three polypeptides: IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1rα). IL-1α and IL-1β are pleiotropic cytokines with a wide range of inflammatory and immunological activities,

while IL-1rα prevents pro-inflammatory functions by acting as a competitive receptor inhibitor. The IL-1 family includes two separate receptors, type 1 and type 2 IL-1 receptors. Specifically, the type 1 IL-1 receptor induces intracellular signal transduction upon binding with IL-1, whereas the type 2 IL-1 receptor functions as a decoy receptor. The complex balance between the molecules and receptors of the IL-1 family significantly impacts TMJ homeostasis. Studies have shown higher levels of IL-1α and IL-1β in the synovial fluid of patients with TMDs.[5] Most IL-1α remains intracellular or on the cell membrane surface, while most IL-1β is transported out of the cell. Elevated levels of IL-1β in the synovial fluid of TMD patients likely originate from synovial and endothelial cells. Significantly high concentrations of IL-1β have been observed in the synovial fluid of TMJs with radiographic evidence of degenerative bone changes, and detectable levels of IL-1β are associated with the extent of radiographic erosion in the TMJ.

IL-6:

IL-6 is a circulating cytokine produced by various cells, including endothelial cells, adipose tissue, T-cells, smooth muscle cells, and macrophages. It initiates the acute phase reaction and primarily regulates the production of hepatic C-reactive protein (CRP). IL-6 is involved in the regulation of oncogenesis, hematopoiesis, inflammation, and immune responses. It also mediates the induction of osteoclast activity and the differentiation of osteoclast progenitors. Notably, IL-6 is crucial in the transition from acute to chronic inflammation, exhibiting a dual impact. IL-6 plasma concentrations can be detected within 60 minutes after tissue injury, peaking between four to six hours and lasting up to 10 days.[6] It acts synergistically with IL-1β. Additionally, IL-11 is a novel cytokine in the IL-6 family that performs similar functions, including influencing osteoclastogenesis.

IL-8:

IL-8 is a chemokine that can induce chemotaxis and activate neutrophils, leading to the infiltration of neutrophils into the synovial fluid and contributing to joint inflammation.[7]

Tumor necrosis factor- α:

TNF is widely recognized as a key pro-inflammatory cytokine, existing in two forms: membrane TNF (mTNF) or pro-TNF, and soluble TNF (sTNF). mTNF, a 26 kDa transmembrane protein, is converted to sTNF by TNF-converting enzyme (TACE). TNF is vital in leukocyte recruitment, monocyte chemoattraction, apoptosis, and the regulation of adhesion molecule expression, exhibiting effects similar to IL-1. Produced by macrophages, TNF stimulates the secretion of collagenase, prostaglandin E2, and interleukins such as IL-6 and IL-8.[8] Elevated levels of TNF-α in TMJ synovial fluid are significantly linked to allodynia, nonchronic pain, and degenerative bone changes. TNF receptors, TNFR-I and TNFR-II, have soluble forms (sTNFR-I and sTNFR-II) found in human serum and synovial fluid. A clinical study found that elevated pretreatment levels of TNF in TMJ synovial fluid were associated with TMJ pain. However, after glucocorticoid intra-articular injections, synovial fluid TNF levels and pain relief were reduced.[9]

SALIVARY MARKERS:

Saliva has gained significant attention as a diagnostic fluid for TMDs due to its non-invasive collection method and its potential to reflect both local and systemic changes.

Oxidative stress markers:

The imbalance between the production of reactive oxygen species (ROS) and the body's

ability to counteract them leads to oxidative stress. Research indicates that oxidative stress can be caused by both inflammatory processes and psychological factors like stress, which are linked to TMD development. It is conceivable that stress exerted on the temporomandibular joint (TMJ) and masticatory muscles may instigate the production of free radicals through various mechanisms. This process has the potential to exacerbate tissue damage, inflammation, and pain. Mechanical tension in the joint can suppress local antioxidant defense, leading to the accumulation of free radicals and damage to the joint tissues. Repeated strain on the muscles causing hypoxia damage can also increase the formation of free radicals and inflammatory mediators. Markers of cell damage caused by ROS have been used to track this process. The overall activity of oxidants and antioxidants can be assessed through the total oxidant status (TOS) and the total antioxidant capacity (TAC), which have been applied in clinical and animal studies to evaluate the overall activity of these molecules. Salivary markers for oxidative stress such as glutathione peroxidase, superoxide dismutase, total antioxidant capacity (TAC), uric acid, 8-OHdG, and MDA, as well as salivary cortisol (SC) as a stress indicator, have been the subject of research. Oxidative changes appear to play a role in the development of pain in TMD. Previous studies have shown reduced TAC in patients with acute pain or inflammation. Inflammation in the TMJ is believed to be associated with oxidative stress as a result of free radical accumulation, leading to tissue damage as part of the inflammatory response. Literature indicates that free radicals and inflammatory mediators are more prevalent in the synovial fluid of TMD patients.[10]

Salivary cortisol:

Salivary cortisol measures the levels of cortisol, a type of steroid hormone, in saliva. Cortisol is a hormone produced by the adrenal glands when the body is under stress, and it plays a role in regulating various bodily functions such as metabolism, immune system activity, and the body's response to stress. Salivary cortisol levels can accurately predict stress and temporomandibular disorders (TMD). Research has demonstrated significant differences in the daily reduction of salivary cortisol between individuals with and without TMD symptoms. Patients with TMD are likely to exhibit higher levels of salivary cortisol in response to the stress caused by TMD-related pain. Da Silva et al.[11] (2012) found a positive correlation between salivary cortisol levels and pain intensity in TMD patients. However, Jasim et al.12 (2018) noted that while cortisol levels were higher in TMD patients, they did not correlate significantly with pain measures, suggesting a complex relationship between stress and TMD symptoms.

Salivary α-amylase

salivary α-amylase is released directly from salivary glands in response to sympathetic nervous system activation. It serves as a marker of autonomic nervous system activity, which may be altered in TMD patients. Kobayashi et al.[13] (2017) observed that α-amylase activity was higher in TMD patients and correlated with self-reported stress levels.

Prostaglandin E2 (PGE2):

PGE2 is synthesized from arachidonic acid via the cyclooxygenase (COX) pathway. It promotes vasodilation, increases vascular permeability, and sensitizes nociceptors. Elevated PGE2 levels contribute to TMJ inflammation and pain. Alstergren et al.[14] tenderness to palpation of the TMJ, and TMJ pressure pain threshold, as well as pain during joint movements (PM (2008) found a correlation between salivary PGE2

concentrations and TMJ pain upon palpation, suggesting its role in pain modulation.

Substance P:

Substance P, released from sensory nerve endings, is involved in neurogenic inflammation and pain signaling. Elevated levels of substance P may indicate heightened nociceptive signaling in temporomandibular disorders (TMDs). Studies found that salivary substance P levels were associated with TMD pain intensity and duration, suggesting its role in pain modulation.[15]

Calcitonin Gene-Related Peptide (CGRP):

CGRP, released from sensory neurons, promotes vasodilation and neurogenic inflammation. Elevated CGRP levels may contribute to TMJ inflammation and pain. Appelgren A et al. observed elevated CGRP levels in the saliva of patients with TMJ arthritis, indicating its involvement in the inflammatory process.[16]

microRNAs (miRNAs):

miRNAs are small non-coding RNAs that regulate gene expression at the post-transcriptional level. They can be released into saliva through mechanisms such as exosome secretion. Changes in miRNA expression may indicate alterations in gene regulation linked to the development of TMD. To date, there are a few published studies evaluating these biomarker profiles in TMD. One study observed decreased expression of miRNA221–3p in synovial fibroblasts from patients with degenerative joint diseases. Researchers found that miRNA221–3p inhibits the transcription of Ets-1, a transcription factor for MMP enzymes responsible for tissue degradation and remodeling in joint cartilage.[17] and investigate function of the specifically selected miRNA in synovial fibroblasts from patients suffering osteoarthritis of temporomandibular joint (TMJOA

DEGRADATIVE ENZYMES:

Degradative enzymes play a vital role in the pathophysiology of temporomandibular joint disorders (TMDs). These enzymes are involved in the breakdown and remodeling of extracellular matrix components in the TMJ, and their dysregulation can contribute to tissue damage and disease progression.

MMPs:

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases essential for the degradation of the extracellular matrix (ECM) and tissue remodeling. Specifically, MMPs 1, 2, 3, 9, and 13 degrade various collagen types found in the TMJ disc and articular cartilage. Elevated levels of these MMPs may indicate ongoing cartilage degradation and synovial membrane remodeling in the TMJ. Nascimento et al.[18] examined the expression of MMP-2 and MMP-9 in the rat trigeminal ganglion during TMJ inflammation. They explored whether mechanical allodynia and orofacial hyperalgesia, induced by injecting complete Freund's adjuvant into the TMJ capsule, were influenced by the MMP inhibitor doxycycline (DOX). Their findings indicated that MMP expression in the trigeminal ganglion varied throughout the inflammatory process, with MMP-9 involved in the early phase and MMP-2 in the later phase. Additionally, increases in mechanical allodynia and orofacial hyperalgesia were reduced by DOX, a non-specific MMP inhibitor. In the context of painful TMD, MMPs are attracting significant interest as potential therapeutic targets for pain management.

Aggrecanases (ADAMTS):

A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS) enzymes, particularly ADAMTS-4 and ADAMTS-5, are key players in proteoglycan degradation.

JPID – The journal of Prosthetic and Implant Dentistry / Volume 8 Issue 2 / January–April 2025

ADAMTS-4 and ADAMTS-5 cleave aggrecan, a key proteoglycan in articular cartilage that provides compressive resistance. Increased aggrecanase activity can lead to loss of cartilage integrity and function in the TMJ. Leonardi et al.[19] (2008) demonstrated increased expression of ADAMTS-4 and ADAMTS-5 in TMJ discs from patients with internal derangement, indicating their role in disc degeneration.

Hyaluronidases:

Hyaluronidases are enzymes that degrade hyaluronic acid, a key component of synovial fluid and articular cartilage. Hyaluronidases break down hyaluronic acid, reducing its viscoelastic properties. Increased hyaluronidase activity may lead to decreased synovial fluid viscosity and impaired joint lubrication in TMDs. Matsumoto T et al.[20] the subcultured TMJ disc cells under both normal and hypoxic conditions (O2: 2% examined HAS3 (hyaluronan synthase) expression in deformed TMJ discs and cells. Immunohistochemistry showed increased HAS3 in diseased discs. In vitro, hypoxia and IL-1β stimulation significantly increased HAS3 mRNA expression in disc cells, particularly at 3 and 24 hours. The results suggest HAS3 is associated with pathological changes in TMJ discs affected by internal derangement.

NEUROTRANSMITTERS:

Glutamate:

Glutamate, an excitatory neurotransmitter, is crucial for nociceptive signaling, with elevated levels indicating increased nociceptive activity in the TMJ area. It can be measured in synovial fluid and microdialysis samples. Alstergren et al.[21] (2010) found that injecting glutamate into a healthy TMJ triggers immediate pain, partly mediated by peripheral NMDA receptors in synovial tissues. Researchers attempted to alleviate TMJ pain by using ketamine or other NMDA antagonists to block these receptors, resulting in partial pain reduction. This highlights glutamate's role in pain processing, though further research is needed to fully understand its role in pain behavior in TMDs, with studies showing a correlation between synovial fluid glutamate levels and TMJ pain upon palpation.

Serotonin

Serotonin is involved in pain modulation and can have both pro-nociceptive and anti-nociceptive effects depending on the receptor subtype activated. Altered levels may reflect changes in pain modulation in TMJ disorders, it can be assessed in synovial fluid and blood. Ernberg et al.[22] (1999) found that local administration of serotonin-induced pain in the masseter muscles of healthy individuals, suggesting its role in TMD pain.

GROWTH FACTORS:

Nerve growth factor

Nerve growth factor (NGF) is a neuropeptide that not only modulates the expression of pain-related markers in both peripheral and central nervous systems but also sensitizes adjacent nociceptive neurons in response to inflammation. Following injury or inflammation to the TMJ, NGF is expressed and initiates signal cascades in peripheral sensory neurons. Several studies have demonstrated elevated levels of NGF in saliva, general circulation, and locally in the synovial fluid of patients with various pain conditions.[23]

Vascular endothelial growth factor:

Vascular endothelial growth factor (VEGF) is a signaling protein released to stimulate angiogenesis in response to inadequate blood circulation, such as during hypoxia. Experimental studies have shown that hypoxia-induced VEGF release is crucial for the recruitment of endothelial

cells, chondrocytes, and osteoclasts. Research has identified increased VEGF expression in condylar cartilage in cases of mechanically induced degenerative joint diseases.[24]

BONE IMAGING MARKERS:

Bone imaging biomarkers are essential in assessing temporomandibular joint (TMJ) disorders, providing crucial insights into structural and functional changes. These biomarkers, derived from various imaging modalities including conventional radiography, CT, CBCT, MRI, bone scintigraphy, and DXA, offer quantitative and qualitative measures of bone quality, morphology, and metabolism. Key biomarkers include joint space narrowing, subchondral sclerosis, osteophyte formation, erosions, condylar volume and shape, bone marrow edema, and bone mineral density. Recent studies have highlighted the utility of these biomarkers: de Oliveira VG et al.[25] (2024) showcased the potential of MRI-based texture analysis (TA) parameters of the condylar medullary bone and the lateral pterygoid muscle (LPM) using MRI to identify changes in individuals with TMD. A comparison of MRI scans from 20 TMD patients and 20 controls showed significant differences in texture parameters, especially in PD(Proton Density-weighted) images. The findings suggest that TA could enhance the accuracy of TMD diagnosis and classification. These imaging biomarkers enable early detection of degenerative changes, assessment of disease severity, and monitoring of treatment outcomes. However, challenges remain in standardization and integration with other clinical data.

NEURO IMAGING MARKERS:

Neuroimaging biomarkers have emerged as powerful tools for understanding the neural mechanisms underlying temporomandibular joint (TMJ) disorders, offering insights into both structural and functional brain changes associated with chronic orofacial pain. These biomarkers, derived from advanced neuroimaging techniques such as functional MRI (fMRI), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS), reveal alterations in brain activity, connectivity, and neurochemistry in TMD patients. Recent studies have highlighted the significance of these markers: Ichesco et al.26 (2021) used resting-state fMRI to demonstrate altered functional connectivity in pain-processing regions, correlating with TMD symptom severity. These neuroimaging biomarkers provide objective measures of central sensitization, pain modulation, and cognitive-emotional processing in TMDs, enabling better characterization of individual patient profiles and potentially guiding personalized treatment approaches.

OTHER POTENTIAL BIOMARKERS:

Collagen markers:

Urinary pyridinoline (PYD) and deoxypyridinoline (DPD) levels were analyzed as potential biomarkers for diagnosing TMJ osteoarthritis (OA) by Ok SM et al.[27] (2018). Significant differences in PYD and DPD concentrations were identified between 36 non-symptomatic subjects and 31 TMJ OA patients, indicating higher sensitivity and specificity in Receiver operating characteristic (ROC) analysis compared to CTX-I and CTX-II. Elevated PYD and DPD levels in TMJ OA patients suggest their potential as supplementary biomarkers for clinical diagnosis.

Hormones:

Hormones are emerging as potential biomarkers for temporomandibular joint (TMJ) disorders, influencing tissue balance and inflammatory responses within the TMJ. Studies, including those by Naqvi, Kapila, Hashem, and Park, have

highlighted the roles of relaxin, estrogen, and progesterone in TMD pathogenesis. Relaxin, particularly potentiated by estradiol, affects matrix remodeling akin to pregnancy, correlating with increased MMP levels like collagenase and stromelysis, and reduced collagen and glycosaminoglycan (GAG) levels in disc samples.[28] Hashem's research additionally noted that progesterone counteracted the effects of relaxin and estrogen, mitigating matrix loss by suppressing MMP induction. These findings underscore the significant hormonal contributions to gender differences observed in TMD.[29]

Lubricin

A compromised lubrication in the TMJ is linked to changes in frictional properties and cartilage surface wear, along with the release of inflammatory and matrix degradation mediators under mechanical loading conditions. Lubricin, among various molecules present in TMJ synovial fluid, plays a crucial role in joint lubrication, especially in boundary lubrication mechanisms. Leonardi R et al.[30] investigated lubricin levels in TMJ SF among patients with Wilkes stages III-V internal derangements (IDs) compared to controls undergoing orthognathic surgery. Significant differences in lubricin levels were observed between ID patients and controls, indicating a potential inverse correlation with age and pain severity (VAS score). These findings underscore lubricin's role in TMJ disease severity and suggest potential biotherapeutic strategies involving lubricin in treatment protocols.

Conclusion:

Biomarkers show great potential in enhancing the management of temporomandibular joint disorders (TMD), though more research is needed to confirm their clinical value. Future studies should explore new biomarkers using advanced proteomics and metabolomics, and develop quick, practical testing methods for clinical use. Non-invasive sampling of saliva, serum, and blood may enable early TMD diagnosis, with current research highlighting potential molecular markers to identify risk factors and predict outcomes. However, challenges remain in standardization, specificity, validation, and integration of biomarkers, as well as addressing current limitations to improve their diagnostic accuracy and clinical utility. Further investigation is needed across diverse, large-scale populations, focusing on heterogeneous models and patients with TMD pain and related conditions. As biomarkers bridge the gap between laboratory research and clinical application, they open the door to a more comprehensive, precise, and individualized approach to oral health care.

References

1. Barkhordarian A, Demerjian G, Chiappelli F. Translational research of temporomandibular joint pathology: a preliminary biomarker and fMRI study. J. Transl. Med. 2020 Dec;18:1-9.
2. Taneja P, Nagpal R, Marya CM, Kataria S, Sahay V, Goyal D. Temporomandibular Disorders among Adolescents of Haryana, India: A Cross-sectional Study. Int J Clin Pediatr Dent. 2019;12:500–6.
3. Shrivastava M, Battaglino R, Ye L. A comprehensive review on biomarkers associated with painful temporomandibular disorders. Int J Oral Sci. 2021;13:1–13.
4. Campos MI, Campos PS, Line SR. Inflammatory cytokines activity in temporomandibular joint disorders: a review of literature. Braz J Oral Sci. 2006 Jul;5(18).
5. Tominaga K, Habu M, Sukedai M, Hirota Y, Takahashi T, Fukuda J. IL-1β, IL-1 receptor antagonist and soluble type II IL-1 receptor in synovial fluid of patients with temporomandibular disorders. Archives of Oral Biology. 2004;49:493–9.
6. de Alcântara Camejo F, Azevedo M, Ambros V, Caporal KST, Doetzer AD, Almeida LE, et al. Interleukin-6 expression in disc derangement of human temporomandibular joint and association with osteoarthrosis. Journal of Cranio-Maxillofacial Surgery. 2017;45:768–74.
7. Sato J, Segami N, Nishimura M, Yoshitake Y, Kaneyama K, Kitagawa Y. Expression of interleukin 8 in synovial tissues in patients with internal derangement of the temporomandibular joint and its relationship with clinical variables. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2007;103:467–74.
8. Black RA, Rauch CT, Kozlosky CJ, Peschon JJ, Slack JL, Wolfson

MF, Castner BJ, Stocking KL, Reddy P, Srinivasan S, Nelson N. A metalloproteinase disintegrin that releases tumour-necrosis factor-α from cells. Nature. 1997 Feb 20;385(6618):729-33.

9. Fredriksson L, Alstergren P, Kopp S. Tumor Necrosis Factor-α in Temporomandibular Joint Synovial Fluid Predicts Treatment Effects on Pain by Intra-Articular Glucocorticoid Treatment. Mediators of inflammation. 2006;2006(1):059425.
10. Kazan D, BAŞ B, Aksoy A, Atmaca E. The evaluation of oxidative stress and inflammation markers in serum and saliva of the patients with temporomandibular disorders. Turkish Journal of Medical Sciences. 2023;53(6):1690-6.
11. Andrade A, Gameiro G, Pereira L, Zanin I, Gavião MB. Salivary cortisol levels in young adults with temporomandibular disorders. Minerva stomatologica. 2008;57:109–16.
12. Jasim H, Louca S, Christidis N, Ernberg M. Salivary cortisol and psychological factors in women with chronic and acute oro-facial pain. J. Oral Rehabil. 2014 Feb;41(2):122-32.
13. Kobayashi FY, Gavião MBD, Marquezin MCS, Fonseca FLA, Montes ABM, Barbosa TDS, et al. Salivary stress biomarkers and anxiety symptoms in children with and without temporomandibular disorders. Braz oral res. 2017;31.
14. Alstergren P, Kopp S. Prostaglandin E2 in temporomandibular joint synovial fluid and its relation to pain and inflammatory disorders. J Oral Maxillofac Surg. 2000;58:180–6.
15. Doshi TL, Nixdorf DR, Campbell CM, Raja SN. Biomarkers in temporomandibular disorder and trigeminal neuralgia: A conceptual framework for understanding chronic pain. Canadian Journal of Pain. 2020 Jan 1;4(1):1-8.
16. Appelgren A, Appelgren B, Eriksson S, Kopp S, Lundeberg T, Nylander M, et al. Neuropeptides in temporomandibular joints with rheumatoid arthritis: a clinical study. European Journal of Oral Sciences. 1991;99:519–21.
17. Xu J, Liu Y, Deng M, Li J, Cai H, Meng Q, et al. MicroRNA221-3p modulates Ets-1 expression in synovial fibroblasts from patients with osteoarthritis of temporomandibular joint. Osteoarthritis and Cartilage. 2016;24:2003–11.
18. Nascimento GC, Rizzi E, Gerlach RF, Leite-Panissi CRA. Expression of MMP-2 and MMP-9 in the rat trigeminal ganglion during the development of temporomandibular joint inflammation. Braz J Med Biol Res. 2013;46:956–67.
19. Leonardi R, Crimi S, Almeida LE, Pannone G, Musumeci G, Castorina S, et al. ADAMTS-4 and ADAMTS-5 expression in human temporomandibular joint discs with internal derangement, correlates with degeneration. Journal of Oral Pathology & Medicine. 2015;44:870–5.
20. Matsumoto T, Inayama M, Tojyo I, Kiga N, Fujita S. Expression of hyaluronan synthase 3 in deformed human temporomandibular joint discs: in vivo and in vitro studies. Eur J Histochem. 2010;54:e50.
21. Alstergren P, Ernberg M, Nilsson M, Hajati AK, Sessle BJ, Kopp S. Glutamate-induced temporomandibular joint pain in healthy individuals is partially mediated by peripheral NMDA receptors. J. Orofac. Pain. 2010 Apr 1;24(2).
22. Ernberg M, Hedenberg-Magnusson B, Alstergren P, Kopp S. Effect of local glucocorticoid injection on masseter muscle level of serotonin in patients with chronic myalgia. Acta Odontologica Scandinavica. 1998;56:129–34.
23. Jasim H, Ghafouri B, Gerdle B, Hedenberg-Magnusson B, Ernberg M. Altered levels of salivary and plasma pain related markers in temporomandibular disorders. The journal of headache and pain. 2020 Dec;21:1-0.
24. Ernberg M. The role of molecular pain biomarkers in temporomandibular joint internal derangement. J. Oral Rehabil. 2017 Jun;44(6):481-91.
25. de Oliveira VG, Correa EC, Costa AL, de Moraes MB, de Castro Lopes SL. Texture analysis as a marker for identifying joint changes in temporomandibular disorders on magnetic resonance imaging. Braz. Dent. Sci. 2024 Jul 1;27(3).
26. Ichesco E, Quintero A, Clauw DJ, Peltier S, Sundgren PM, Gerstner GE, Schmidt-Wilcke T. Altered functional connectivity between the insula and the cingulate cortex in patients with temporomandibular disorder: a pilot study. Headache: The Journal of Head and Face Pain. 2012 Mar;52(3):441-54.
27. Ok SM, Lee SM, Park HR, Jeong SH, Ko CC, Kim YI. Concentrations of CTX I, CTX II, DPD, and PYD in the urine as a biomarker for the diagnosis of temporomandibular joint osteoarthritis: A preliminary study. Cranio. 2018;36:366–72.
28. Puri J, Hutchins B, Bellinger LL, Kramer PR. Estrogen and inflammation modulate estrogen receptor alpha expression in specific tissues of the temporomandibular joint. Reprod Biol Endocrinol. 2009;7:155.
29. Hashem G, Zhang Q, Hayami T, Chen J, Wang W, Kapila S. Relaxin and β-estradiol modulate targeted matrix degradation in specific synovial joint fibrocartilages: progesterone prevents matrix loss. Arthritis Res Ther. 2006;8:R98.
30. Leonardi R, Perrotta RE, Almeida LE, Loreto C, Musumeci G. Lubricin in synovial fluid of mild and severe temporomandibular joint internal derangements. Med Oral Patol Oral Cir Bucal. 2016;21:e793–9.