REVIEW

Biomarkers and their impact on Temporomandibular Disorder: A narrative review

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Abstract

Termperomandibular Disorders encompass a group of musculoskeletal and neuromuscular conditions affecting the temporomandibular joint and associated structures, leading to pain, functional limitations and psychological distress. The variety of TMD symptoms leads to several diagnostic challenges, which can be illustrated by difficulties in treatment planning. Biomarkers are biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. They enhance our ability to identify relationships between environmental chemicals and human diseases, thereby improving our capacity to diagnose, monitor, or predict disease risk. They can serve as an early warning systems for our health. They are often measured and evaluated using blood, synovial fluid, saliva, and other bodily fluids to examine normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. These biomarkers are a relatively new clinical toolset categorised by their clinical applications. This article presents a review on the impact of various biomarkers on TMD.

Keywords: TMD, Biomarkers, Diagnosis

Introduction

Biomarkers are objective measurements that capture the current state of an organism or cell. They enhance our ability to identify relationships between environmental chemicals and human diseases, thereby improving our capacity to diagnose, monitor, or predict disease risk. They can serve as an early warning systems for our health. Biomarkers are often measured and evaluated using blood, synovial fluid, saliva, and other bodily fluids to examine normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[1] These biomarkers are a relatively new clinical toolset categorized by their clinical applications. The four main classes are molecular, physiologic, histologic and radiographic biomarkers. All four types of biomarkers have a clinical role in narrowing or guiding treatment decisions and follow a sub-categorisation of being either predictive, prognostic, or diagnostic.[2]

Pathophysiology & Diagnostic challenges in TMD

Temporomandibular disorder (TMD) is a musculoskeletal disorder that is manifested through continuous pain in the temporomandibular joint (TMJ), masticatory muscle, and the periauricular region.[3] Meanwhile, the most common non-odontogenic orofacial pain is a pain in the temporomandibular area.[4,5] Other related symptoms like hyoid bone tenderness, abnormal swallowing, and tinnitus have an impact on an individual's sleep, quality of life, and psychological well-being.[6] Therefore, these symptoms also result in depression, stress, anxiety, adverse impacts on energy level, emotional condition and social function.[7,8] The occurrence of TMD symptoms ranges from 21.5% to 50.5%, with women experiencing more than men[6]. Constitutional, hormonal, psychological, biological, anatomical, and behavioural factors are the causes of this discrepancy.[9,10,11] The pathophysiology of TMD is multifactorial, which includes biopsychosocial, neuromuscular, biomechanical, and biological factors. [6,12]

The variety of TMD symptoms leads to several diagnostic challenges, which can be illustrated by difficulties in treatment planning.[13] In most cases, diagnosis is based on history physical & radiographic examination.[14] Orthopentogram (OPG), Lateral Cephalogram, Computed Tomography (CT) are commonly used. However to become radiographically evident considerable amount of bone loss around 30% should happen.[15] Therefore, some new diagnostic approaches should be considered which might help in early detection of bone disorders.

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Diagnostic Biofluids : From Synovial fluids to Saliva

Biomarkers are analyzed using biological samples such as tissue biopsy and biofluid plasma, saliva, synovial fluid, and cerebrospinal fluid. Previously, blood serum was the gold standard for biomarker assessment and validation, and this was followed by synovial fluid. Joint specific biochemical indicators cannot enter the bloodstream because the synovium, the semi-permeable barrier lining the synovial joint naturally blocks the passage of large molecules. Hence, synovial fluid analysis can uniquely pinpoint joint conditions, providing real-time information.[16] One study unveiled a correlation between specific TMD biomarkers and morphological variations in distinct anatomical regions of the TMJ condylar surface and stated that the condyle's front surface had shown bone apposition and repair, while regions of bone resorption were specifically observed near the lateral pole.[17]

In recent years, there has been growing interest in exploring the potential role of salivary biomarkers in TMDs.[18,19,20] Saliva, as a readily accessible biofluid, offers numerous advantages as a diagnostic medium, such as noninvasiveness, cost-effectiveness and ease of collection. Furthermore, saliva plays a critical role in maintaining a protective barrier over oral tissues, which helps mitigate mechanical stress and friction during mastication.[24,25,26,27,28]

Saliva is also essential for lubricating the temporomandibular joint (TMJ) during movement. Changes in saliva's pH and buffering ability can alter the oral environment.[34] Acidic surroundings can cause enamel demineralisation, which can exacerbate symptoms of TMD.35 Even a decrease in salivary flow or a change in the content of the saliva could cause insufficient lubrication, which would increase friction and damage the TMJ structures.[33]

Salivary biomarkers, such as proteins, enzymes, inflammatory mediators and genetic markers, hold promise as objective indicators of disease presence, progression and treatment outcomes in TMDs.[21,22,23] According to new research, the pathophysiology of painful

TMD might be due to inflammation or the release of inflammatory cytokines, possibly due to mechanical overload, local hypoxia, microtrauma, and reduced adaptive capacity of cartilage.[16] By examining the molecular signatures present in saliva, researchers aim to unravel the complex pathophysiological processes associated with TMDs and identify novel diagnostic and therapeutic targets. In this context, saliva has emerged as a promising medium for obtaining a real-time biomarker.[29,30,31,32,36,37]

A list of various biomarkers and their consequent actions on TMD has been summarized in Table 1. Accordingly, this article aims to provide a comprehensive review of recent updates on TMD biomarkers, focusing on their diagnostic utility as well as their promising potential for suppressing inflammation and eliminating pain

Molecular Profiling of TMD Biomarkers

4.1 Prostaglandins

They are synthesized via the cyclooxygenase (COX) enzymatic pathway during acute and chronic tissue stress, PGE2 is a primary mediator of inflammatory hyperalgesia.[16] Elevated levels of PGE2 in the synovial fluid of TMD patients correlate significantly with reported TMJ pain during mandibular movement.[38] This correlation underlines its clinical value as a functional marker of localized joint inflammation.

4.2 Cytokines

They are the essential polypeptide mediators of critical and severe inflammation.[39] These molecules function as complex immunological networks containing pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF), and anti-inflammatory mediators, such as interleukin -10 (IL-10) and transforming growth factor-beta (TGF-β). The balance between them dictates either joint homeostasis or progressive degradation. The high concentrations of pro-inflammatory cytokines are strongly linked to osteoarthririts (OA) and internal derangement (ID).[40] These mediators contribute to the degradation of cartilage and bone joints by releasing proteinases and other inflammatory molecules.

- **Interleukin 1 (IL-1):** The IL-1 family includes the pro-inflammatory ligands IL-1α and IL-1β, balanced by their competitive receptor antagonist, IL-1ra.[41] An imbalance favoring elevated synovial IL-1α and IL-1β concentrations disrupts TMJ metabolic homeostasis, triggering the development and accelerating the severity of structural TMD.[42]
- **Interleukin 6 (IL- 6):** IL-6 is a circulating cytokine produced by cells (endothelial cells, adipose tissue, T-cells, smooth muscle cells, and macrophages).[43] It regulates oncogenesis, hematopoiesis, and immune responses.[44] Crucially, it acts as a primary molecular bridge driving the transition from acute to chronic inflammation by inducing osteoclast progenitor differentiation and activating localized bone resorption.[45] Following acute tissue injury, systemic plasma concentrations of IL-6 rise within 60 minutes, peaking between 4 to 6 hours and persisting for up to 10 days.[46,47] Due to its broad systemic involvement in hematopoiesis and oncogenesis, isolating an IL-6 reading to confirm a specific diagnosis of TMD requires localized synovial fluid sampling, which is heavily limited by clinician technique and patient discomfort
- **Interleukin 8 (IL- 8):** IL-8 is produced by macrophages, endothelial cells, and epithelial tissues.[48] It induces targeted chemotaxis and recruits neutrophils into the synovial fluid,[49] exacerbating active joint inflammation especially in angiogenic diseases, including rheumatoid arthritis (RA).[50,51] This chemokine is highly sensitive to local tissue hypoxia,[52] and its presence has been verified at the posterior disc attachment in patients diagnosed with internal derangement.[53] It also leads to increase in the amount of inflammatory cells in TMJ.[54,55] Because IL-8 is heavily dependent on localized hypoxia as a regulatory trigger, its presence is highly variable. It may drop below detectable diagnostic thresholds in chronic, non-inflammatory myofascial TMD or stabilized disc displacements where active tissue strain has subsided.

Table 1 Biomarkers and their actions

Thamer, S.R. and Diajil, A.R. (2024)[98]	Saliva	MMPs	MMP-2 and MMP-9 positively correlated with pain and joint click and negatively with mouth opening.
AlSahman, L. et al. (2024)[99]	Saliva	Cortisol	↑cortisol: Disc Displacement without Reduction
Ismah, N. et al. (2024)[100]	Saliva	IL-1β	Pain-related or joint TMDs
Kim, Y. et al. (2023)[101]	Blood	ILs, Cortisol	↑IL-1β, ↑IL-4, ↑IL-8, and ↑IL-17 showed sufficient strength
Ornek et al .(2023)[102]	Saliva	Cortisol, IL-1β, TNF- α and MMP3	Although not significantly greater, cortisol and depression/anxietywere higher in the study group. Additionally, there was no discernible difference in the others
Shao, B. et al. (2023)[103]	Synovial fluid	ILs, PGE2	High levels of biomarkers, Osteoarthritis > Disc Displacement
Aparna, N. et al. (2023)[104]	Saliva	Cortisol	No statistically significant difference in salivary cortisol level between cases and controls.
Kazan, D. et al. (2023)[105]	Saliva, blood	IL-6,	Strong positive correlation between pain
Zwiri, A.M. et al. (2022)[106]	Blood	ILs	IL-8 may serve as a potential biomarker for TMJ pain:
Ulmner, M. et al. (2022)[107]	Synovial fluid	ILs, TNF-α	IL-1β and TNF-α were significantly associated with TMJ palpation pain. TNF-α also correlated with subjective TMJ pain. IL-1β was linked to synovitis, which contributes to pain
Bayındır, S., et al. (2022)[108]	Synovial fluid	PGE2	PGE2 are linked to localized TMJ pain and are elevated in joints with degenerative changes
Venkatesh, S.B. et al. B. et al. (2021)[109]	Saliva	Cortisol	Cortisol: strong association with stress and TMD severity.
Son, C. et al. (2021)[110]	Blood	ILs, TNF-α, PGE2,	TMD—higher pain intensity/duration and ↑IL-8 and IgG levels link chronic pain and systemic inflammation.
Ulmner, M. et al. (2020)[111]	Synovial fluid	ILs	Disc Displacement without Reduction: IL-1↑ (female > male)
Loreto, C. et al. (2020)[112]	Synovial fluid	MMPs	MMP-7 and MMP-9 overexpressed in Disc Displacement without Reduction
Khayam et al. (2020)[113]	Saliva	Cortisol	In comparison to the Control group, the TMD group had considerably higher levels of cortisol .
Shoukri et al. (2019)[114]	Saliva	MMP3, PAI-1 IL1α, IL6, MMP 3, MMP7, PAI-1, TNFα	MMP- 3, and PAI- 1 were positively expressed and significantly correlated to condylar variance in TMD patients among all the biomarkers evaluated.
Xiong et al. (2019) [115]	Synovial fluid	IL6	Elevated leptin levels in temporomandibular joint promote proinflammatory cytokine IL-6 expression in synovial fibroblasts
Yang et al. (2019)[116]	Synovial fluid	IL8	MRI- levels of cytokines (IL-8, and TNF) in the synovial fluid were increased in TMD cases
Ganti, S. et al. (2018)[117]	Synovial tissue	ILs, TNF-α, PGE2	IL-1β, TNF-α, PGE2, and IL-6- TMD
Ce et al. (2018)[118]	Saliva	IL-1β	Regardless of a fibromyalgia assessment, the patients with TMD alone had significantly higher IL-1 levels, whereas the group with fibromyalgia alone did not differ significantly from the Control Group
Watanabe et al., (2017) [119]	Synovial fluid	IL-1β, IL-6, and IL-8	Protein concentrations of IL-1, IL-6, and IL-8 ↑ - ELISA Test- inflammatory condition in the TMJ.
Kobayashi et al (2017) [120]	Saliva	Cortisol	Cortisol levels were assessed to not be significantly linked to TMD, although anxiety related symptoms were more severe in the TMD group

Dawson et al (2016) [121]	Synovial fluid	Dopamine	In myofascial pain and degenerative diseases, dopamine might be involved in modulating peripheral pain
Ahmed et al. (2015) [122]	Synovial fluid	TNF	TMJ pain -increased inflammatory activity
Lin, S.L., et al. (2015) [123]	Blood	Cortisol	↑Cortisol in Disc Displacement without Reduction: clinical indicator for distinguishing disc displacement disorders
Cevidanes, L.H. et al. H. et al. (2014) [124]	Synovial fluid and blood	MMPs, ILs, TNF	Osteo Arthritis showed bone resorption: MMPs linked to bone apposition, while IL-6 and TNFα linked to bone resorption.
Vos, L.M. et al. (2013) [125]	Synovial fluid	IL-1β, TNF-α, PGE2	High collagen-II levels suggest it may be a useful marker for cartilage degradation.
Wake et al. (2013) [126]	Synovial fluid	IL-6	Concentrations of aggrecan, IL-6, and VEGF-A were significantly higher in the group with synovial chondromatosis of TMJ
Nogami et al. (2013) [127]	Synovial fluid	IL-6	Concentration of IL-6 were significantly higher in patients with joint effusion
Kim et al. (2012) [128]	Synovial fluid	IL-1β, IL-2, IL-6, IL-8, IL-10, and TNF-α	interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10 and tumour necrosis factor (TNF)-α were detected in the TMD
Slade, G.D. et al. D. et al. (2011). [129]	Blood	ILs	Localized TMD linked to IL-1 and widespread TMD linked to IL-8.
Miller, K. E et al (2011). [78]	Synovial fluid	Glutamate	Involved in pain processing, peripheral nociception, and central sensitization of painful TMD
Alstergren, P et al .(2010) [80]	Synovial fluid	Glutamate	Glutamate evokes immediate pain in the healthy human TMJ that is partly mediated by peripheral NMDA receptors in the TMJ.
Lee et al. (2010) [130]	Synovial fluid	IL-6 and TNF-α	Elevation of TNF-alpha and IL-6, in the synovial fluid of temporomandibular disorder patients with symptoms of pain, mouth opening limitation, and clicking.
Hamada et al. (2008) [131]	Synovial fluid	IL-6, IL-8 & IL10	Presence of IL-10 i is a significant predictor of successful outcome of TMJ irrigation for Chronic Closed Lock
Vernal et al. (2008) [132]	Synovial fluid	IL-1b, IL-2, IL-12, TNF-α and TNF-β	IL1β , TNF-α , IL10, IL12, and IL17 are involved in the OA-TMJ pathogenesis
Sato, J. et al. (2007)[54]	Synovial fluid	IL 8	↑IL-8 in TMD, no significant link to pain or inflammation severity
Yoshida, K. et al. (2006) [68]	Synovial fluid	MMPs	↑MMP-9 in severe TMJ Osteoarthritis and disc displacement. ↑MMP-2 elevated in early Osteoarthritis.
Kardel et al (2006) [133]	Synovial fluid	IL-1α, IL-1β	The cytokines (IL-1α, IL-1β) ↑ in TMD
Matsumoto et al., (2006) [134]	Synovial fluid	IL8	Elevated cytokine levels in TMD
Kaneyama, K. et al. (2004) [135]	Synovial fluid	ILs	↑IL-6 and ↑IL-11 in joints with condylar bone changes: osseous degeneration.
Nishimura et al., (2004) [136]	Synovial fluid	IL-1α, IL-1β,	Presence of IL-1β and IL-6 in synovial fluid are indicators for internal derangement of the TMJ.
Kardel, R. et al. (2003) [137]	Synovial fluid	ILs, TNF-α	Osteoarthririts joints: ↑IL-1α, ↑IL-1β
Nishimura et al., (2002) [77]	Synovial Fluid	Bradykinin	Involved in TMD pain secondary to disc disorders degenerative joint diseases and muscle soreness
Srinivas, R. et al. [72]	Synovial fluid	MMPs	↑MMP-1, ↑MMP-2, ↑ MMP-8, ↑MMP-9 ↑, MMP-13 in mild TMJ-ID—active collagen degradation
Tanaka, A. et al. (2001) [138]	Synovial fluid	MMPs	↑MMP-2 and ↑MMP-9 in Disc Displacement without Reduction > Disc Displacement with Reduction—diagnostic markers.

Shinoda et al (2000) [139]	Synovial fluid	IL6	IL-6 - chronic TMJ disorders
Ernberg et al (2000) [89]	Synovial Fluid	Serotonin	Involved in Peripheral and cental pain mechanism of painful TMD. Sensitize neuropeptides and other neurotransmitters such as glutamate are involved in the modulation and control of TMD pain.
Murakami, K.I. et al. (1998) [140]	Synovial fluid	PGE2	↑PGE2 linked to TMJ degeneration
Kubota, E. et al (1998) [141]	Synovial fluid	MMPs and ILs	IL-1β ↑Disc Displacement without Reduction, IL-1β ↑Osteoarthriris, IL-6 ↑Osteoarthritis —markers linked to cartilage degradation and pain in TMD
Takahashi et al. (1998) [142]	Synovial Fluid	IL-1β, and TNF-α	Increased levels of proinflammatory cytokines IL-1β in TMD ,
Kubota, E. et al. (1997) [143]	Synovial fluid	IL-1β, MMP, TNF-α	↑IL-1β in TMD (osteolytic changes TMJs) ↑MMP-3 linked to cartilage degradation —early markers of TMJ deterioration and pain.
Fu et al. (1995) [144]	Synovial Fluid	TNF-α & IL6	Increased in TMD

- **Tumour Necrosis Factor (TNF):** TNF is regarded as the master pro-inflammatory cytokine.[56] It is present in the form of membrane TNF (mTNF), pro-TNF and soluble TNF (sTNF).[57,58] Specifically, mTNF is a transmembrane protein which is transformed into sTNF when divided by TNF-converting enzyme (TACE).[57,59] Furthermore, TNF plays an essential role in leukocyte recruitment, monocyte chemo-attraction, development of apoptosis, and enhanced management of adhesion molecule expression.[60] Immune cells, such as natural killer (NK) cells, activated macrophages/monocytes and activated T cells, and other non-immune cells, such as fibroblasts and endothelial cells, represent TNF.[61] TNF instigates a broad inflammatory cascade by driving the subsequent transcription of downstream mediators like IL-1 and IL-6.[62,63] Clinically, synovial TNF concentrations serve as a valuable predictive biomarker.[64] Another study examined the role of TNF in synovial fluid as a predictor of the therapeutic effect of intra-articular glucocorticoid injection on TMJ in TMD patients and a positive correlation was found in patients with TMD and TNF with chronic inflammatory connective tissue disease.[65] Consequently, a clinician cannot use a positive TNF reading to conclusively diagnose primary TMD unless comprehensive systemic rheumatologic screenings are completed to rule out broader cross-reactive conditions.

4.3 Proteinases

These enzymes hydrolyse peptide links to break down proteins. Matrix Metalloproteinases (MMPs) are tissue-degrading proteolytic enzymes deeply involved in TMJ inflammation and pain.[66] Research shows that joint inflammation upregulates MMP-1, MMP-2, and MMP-13, accelerating degenerative changes and pain progression.[67-69] In patients with disc disorders and joint degeneration, TMJ synovial fluid contains elevated levels of collagenases (MMP-1, MMP-8, MMP -9, MMP -13), stromelysin (MMP-3), and gelatinases (MMP-2, MMP-7).[70-74] This expression is also influenced by psychological stress, which elevates MMP-3 levels in correlation with TMD severity.[75] Furthermore, MMP-2 and MMP-9 have been detected in the trigeminal ganglion during TMJ inflammation.[76] Ultimately, these enzymes serve as viable therapeutic targets for TMD pain management.

4.4 Neuropeptides

These are small protein-like molecules, specifically short chains of amino acids, that act as signalling molecules in the nervous system and other tissues. They are synthesized and released by neurons and play a crucial role in various physiological processes like pain perception, stress response, etc. Bradykinins are mediators of inflammation, which are crucial for nociception and sensitisation. It is a powerful vasodilator and promoter of vascular permeability, elevated synovial bradykinin levels correlate positively with verified degrees of joint inflammation in patients with structural disc disorders.[77] This provides excellent diagnostic sensitivity for identifying active internal joint derangements.

4.5 Neurotransmitters

These are chemical messengers that carry messages from neurons to other cells, such as muscles or glands, across synapses. Neurotransmitters are important for both central processing and peripheral or central sensitisation in painful TMDs. They have a significant influence on mood and behavior in addition to pain processing.

- **Glutamate :** Glutamate acts as the primary excitatory neurotransmitter within afferent sensory nerves, it relays peripheral pain data from the TMJ and trigeminal ganglion straight to the central nervous system

(CNS).[22] Glutamate is highly sensitive to painful TMD states, accumulating significantly in the synovial fluid of joints undergoing advanced degenerative diseases secondary to rheumatoid arthritis.[78,79,80] However, because glutamate can easily leak into synovial tissues directly from the plasma during systemic excitatory states, its absolute diagnostic specificity for primary isolated joint pathology can be compromised limiting its use to specialized diagnostic centers.

- **Dopamine:** Dopamine participates in a complex regulatory balance governing motor control, cognition, and nociceptive processing across both the central and peripheral nervous systems. In patients presenting with myofascial pain TMD (M-TMD), peripheral plasma dopamine levels rise significantly[81] and correlate tightly with masticatory muscle pain intensity and elevated levels of perceived mental stress.[82,83] Plasma dopamine acts as a sensitive index of patients overall psychological distress and systemic sympathetic nervous system activation. It exhibits high sensitivity for mapping masseter muscle pain intensity.[84] However, it has very low specificity for structural joint pathology.[85] Because central dopamine neurotransmission changes during any chronic pain condition , plasma dopamine readings cannot be used to diagnose TMD independently; they must be interpreted alongside a comprehensive physical and psychological evaluation.
- **Serotonin:** Serotonin or 5-hydroxytryptamine (5-HT) modulates physiological processes in both the central and peripheral nervous systems. It is observed that in response to tissue trauma and inflammation, 5-HT3, a subtype of 5-HT, is released and sensitizes peripheral neurons, which seems to be important for mediating pain from the periphery.[86,87] Patients with chronic myalgia exhibit an increased density of these serotonin receptors directly on the sensory nerves of the masseter muscle.[88,89] Serotonin is an exceptionally robust diagnostic biomarker as it is completely undetectable in the TMJ synovial fluid of healthy individuals . Consequently, the mere emergence of serotonin in synovial fluid provides nearly 100% diagnostic specificity for joint pathology. Elevated levels in the synovial fluid, serum, and saliva correlate with mechanical jaw movement pain, chronic myalgia, and localized allodynia.[87,88,89,90] Furthermore, local and systemic 5-HT levels partially determine the therapeutic success of intra-articular glucocorticoid injections for TMJ pain, making serotonin a highly reliable biomarker for painful TMD.[91] While its presence in synovial fluid is definitive for pathology, its systemic presentation in serum and saliva can be altered by unrelated emotional disorders or medications (such as antidepressants), necessitating careful pharmacological charting during patient intake.

4.6 Salivary Cortisol

Cortisol, known more formally as hydrocortisone, is a steroid hormone, more specifically a glucocorticoid, produced by the zona fasciculata of the adrenal cortex. Its main actions include suppressing the immune system, promoting the metabolism of fat, protein, and carbohydrates, and raising blood sugar levels through gluconeogenesis. It also decreases bone formation.[92,93] TMD patients are likely to present higher salivary cortisol levels as a response to the stress of TMD pain.[94] Furthermore, it has been demonstrated that a greater cortisol level is connected with a higher Visual Analogue Scale (VAS) score.[95] Additionally, salivary cortisol levels were found to be significantly higher in patients with disc displacement without reduction and limited mouth opening.[96] Despite its ease of collection and analytical clarity, cortisol secretion follows a strict diurnal rhythm, peaking immediately upon waking and tapering throughout the day. To maintain diagnostic accuracy and avoid false positives or negatives, saliva sampling must be strictly standardized to specific collection times, and clinicians must control for confounding variables such as acute sleep deprivation or systemic steroid therapy.

Future perspectives

The biomarkers help to map a patient's profile by providing an invaluable clinical toolset that addresses traditional diagnostic challenges. These molecular messengers reveal early signs of localized disease, underlying risks, and actual treatment responses. Gene mapping in TMD could be a future diagnostic tool in identifying inherited gentic variant that may cause joint pain & inflammation. This is possible because the TMJ's connective tissues and cartilage uniquely develop from neural crest cells rather than the mesoderm.[97]

Conclusion

TMDs are among the most common maxillofacial disorders, despite the various diagnostic procedures involved, the biomarker profile of patients with TMDs serves as a critical diagnostic tool.

The pathophysiology of painful TMD involves a shift from localized inflammation and cartilage degradation to broader neuroendocrine involvement in chronic states. While acute painful TMD is heavily characterized by inflammatory cytokines, prostaglandins, and matrix metalloproteinases driven by mechanical stress, chronic cases are further compounded by alterations in neurotransmitters, neuropeptides, and cortisol levels.

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