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Editorial

Biomarkers associated with Temporomandibular Disorders: Current Status and Prospective Paths

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Chronic discomfort in the temporomandibular joint (TMJ), masticatory muscles, and periauricular area are the hallmarks of temporomandibular disorder (TMD). In the meanwhile, temporomandibular pain is the most frequent cause of non-odontogenic orofacial pain. Sleep, quality of life, and psychological well-being are all adversely affected by additional associated symptoms, such as tinnitus, abnormal swallowing, and bone tenderness in the hyoid bone. Consequently, these symptoms also lead to negative effects on energy level, emotional state, social function, stress, and sadness. TMD symptoms can affect anywhere from 21.5% to 50.5% of people, with women more likely than males to experience them. In addition to being difficult to diagnose, the right course of treatment for TMJ disorders is also debatable. Furthermore, the variations in TMD results between the people at different times lead to additional problems with TMD diagnosis. To create an appropriate treatment plan in response to the confirmed diagnosis, adequate knowledge is essential.[1]

Biomarker refers to "a characteristic that is objectively measured and evaluated as an indicator of normal biological process, pathogenic processes, or pharmacologic responses to a therapeutic intervention". An ideal biomarker should have a number of essential characteristics, including high sensitivity and specificity, which must be present in all diagnosed patients, the ability to detect disease specificity before obvious clinical symptoms appear, and the ability to reverse the effects of the disease with the right care. The ideal biomarkers should allow for a cut-off value with little overlap between the state of normal health and disease, as well as information displaying the cumulative history of the illness in addition to indicating the severity of the illness. Furthermore, it was discovered that several types of synovial, serum, and urine proteins demonstrated significant TMD diagnostic value.[2]

The primary polypeptide mediators of severe and critical inflammation are called cytokines. These molecules operate as intricate networks of immune cells that include pro-inflammatory cytokines (TNF, IL-6, and interleukin 1 (IL-1), as well as anti-inflammatory mediators (IL-10) and transforming TGF-beta (transforming growth factor-beta). Internal derangement (ID) and Osteoarthritis (OA) are two TMD symptoms that are typically linked to high levels of pro-inflammatory cytokines, despite a number of contentious findings about cytokines. Through the release of proteinases and other inflammatory chemicals, these mediators lead to the degradation of bone joints and cartilage. A study conducted by Ok et al. 2018[4] revealed that patients with TMDs had higher levels of urine deoxypyridinoline (DPD) and pyridinoline (PYD). Furthermore, according to Slade and his colleagues analysis of TMD patient blood samples, demonstrated a notable rise in TGF-1, IL-8, IL-1 receptor antagonist (IL-1ra), and monocyte chemotactic protein (MCP-1) [41]. Overall, it is evident that since 1995, research has focused on these TMD biomarkers; the most promising biomarkers were found to be IL-6, IL-8, IL-1, and TNF.[3,5]

IL-8 is produced by macrophages and other cells, such

as endothelial, smooth muscle, and epithelial cells in the airway [69]. Previously recognised as monocyte-derived neutrophil chemotactic factor or neutrophil-activating protein-1, IL-8 is a chemokine that can trigger neutrophil activation and chemotaxis. It has been discovered that IL-8 plays a role in both joint inflammation and neutrophil infiltration into synovial fluid. In ID cases, TMJ inflammation may be followed by the generation of inflammatory cells in the TMJ due to IL-8.

Certain cells including endothelial cells, adipose tissue, T-cells, smooth muscle cells, and macrophages produce the circulating cytokine IL-6. It supports the development of myeloid cells, the expansion of smooth muscle cells, and the synthesis of acute-phase proteins. Consequently, IL-6 was considered one of the key proinflammatory cytokines that contribute to the pathophysiology of ID-related TMJ. Notably, and with a dual effect, IL-6 is a crucial component in the transition from acute to chronic inflammation. The main pro-inflammatory cytokine that contributes to the pathophysiology of TMDs and inflammation is IL-6.

There are at least 21 distinct molecules that collectively make up the IL-1 system, and these molecules combine to produce IL-1 receptors, co-receptors, legends, and endogenous antagonists. There are three types of legends in the IL-1: IL-1 alpha, IL-1 beta, and IL-1ra. Specifically, pro-inflammatory effects are caused by IL-1 alpha and IL-1 beta, but pro-inflammatory effects are inhibited by IL-1ra through its activity as a competitive receptor inhibitor. Many studies have demonstrated the presence of increased levels of IL-1 alpha and IL-1 beta in the synovial fluid of individuals with TMDs, implying the intricate balance between the molecules and receptors of the IL-1 family profoundly affecting TMJ homeostasis.[1,3,6]

The primary pro-inflammatory cytokine has been identified to be TNF. Leukocyte recruitment, monocyte chemo-attraction, apoptotic formation, and improved adhesion molecule expression regulation are all facilitated by TNF. TNF is a combination of immune cells, including natural killer (NK) cells, activated T cells, activated macrophages/monocytes, and other non-immune cells, including fibroblasts and endothelial cells. One of the first cytokines to emerge from the inflammatory stages is TNF, which enhances the synthesis of cascade and other inflammatory mediators, including transcription factors, interleukin IL-1, and IL-6. TNF receptors fall into two categories: TNFR1 and TNFR2, which have distinct intracellular regions and are confined at the cellular surface. TNFR1 is the main mediator of TNF-induced apoptosis while TNFR2 is represented by immunosuppressive cells, especially regulatory T cells (Tregs). Further investigations on patients with chronic inflammatory connective tissue disease and its relationship to TMJ pain revealed a positive correlation between TNF levels and TMJ discomfort.[3,6]

Among the inflammatory mediators, bradykinin is crucial for nociception and sensitization. It's a strong bronchoconstrictor and vasodilator that promotes vascular permeability and eases the transmission of pain. High levels of bradykinin were positively linked with the level of inflammation in a study on TMJ disc problems. PGE2 levels in the synovial fluid of individuals with chronic inflammatory joint disease were found to be elevated, and this association was linked to discomfort in the TMJ during mandibular movement.[6]

Neurotransmitters are crucial for both central processing and peripheral or central sensitization in painful TMDs. Monoamine neurotransmitters, including glutamate, dopamine, and serotonin (5-HT), are currently being investigated as potential biomarkers for painful TMD disorders.

Apart from its involvement in motor control, cognition, and the reward system, dopamine also plays a role in pain perception. Dopamine is mostly synthesised by dopaminergic neurons in the central nervous system, while dopamine is produced in the peripheral nervous system by neuroendocrine cells and the adrenal medulla. A more recent study revealed that plasma dopamine levels were significantly increased in TMD patients, whilst there was no difference in 5-HT levels between patients with myofascial TMD and healthy controls.

Neural growth factor (NGF) is a well-known neurotrophin family member that acts as a mediator for chronic pain. Generally speaking, NGF is expressed following a TMJ injury or inflammation and initiates signal cascades at the peripheral sensory neurons.

Many researchers have focused their attention on the field of epigenetics in chronic pain in an attempt to better understand pain chronification. MicroRNAs, a subclass of short non-coding inhibitory RNAs, have been observed to have a significant impact on the

regulation of pain processing in a variety of clinical pain disorders and experimental models. The miRNA 140-5p, that is expressed in TMJ disc disorders, has been investigated by researchers. They proposed that miR-140-5p could be a unique prognostic factor of TMJ degenerative disorders and regulate mandibular condylar cartilage homeostasis. Furthermore, they proposed that miR-101a-3p and miR21-5p were both implicated in the breakdown of the cartilage matrix and the progression of degenerative changes in TMJ.[6]

Certain areas of the brain can serve as biomarkers for painful TMD because they specifically exhibit changes in these regions. Therefore, researchers have employed a tempting technique called neuroimaging to investigate those biomarkers. Neuroimaging studies the anatomy, physiology, and alterations in neurochemicals in the brain, which may serve as a biomarker for excruciating TMD. To explore changes in the brain in individuals with chronic pain, functional and structural magnetic resonance imaging (fMRI), sMRI, and magnetic resonance spectroscopy (MRS) techniques have been employed extensively, either alone or in combination.6

Salivary biomarkers have emerged as a valuable diagnostic tool in TMDs. Several investigations have demonstrated higher levels of IL-1, glutamate, cortisol, and SAA (Salivary alpha amylase) in TMD patients. These findings suggest that there may be biological mechanisms underpinning the pathophysiology of TMD. These results provide opportunities for more research into the function of these biomarkers in the onset, progression, and mechanisms of pain associated with TMD. Furthermore, changes in biomarkers including PA (Phenylacetate), DMA (Dimethylamine), maltose, acetoin, isovalerate, and oxidative stress markers (such 8-OHdG) can reveal information about possible microbial and metabolic dysregulation as well as oxidative damage in individuals with TMDs. Health care professionals can obtain non-invasive, easily accessible diagnostic indicators through the identification of salivary biomarkers linked to TMDs, facilitating early detection and intervention.[7]

Further investigation is required to determine whether these putative biomarkers can meet practical and reliable requirements for replication of research on large-scale, heterogeneous sample sizes. Future studies on heterogeneous models and people with TMD pain and other concomitant diseases are required to further understand clinical and experimental biomarkers. Based on neural recordings, machine learning techniques have produced encouraging results in predicting human and animal pain states. Moreover, the identification of novel biomarkers will contribute significantly to our knowledge of the pain pattern associated with TMDs and help create therapeutic approaches that can be used in conjunction with TMD treatment.

References:

1. Zakrzewska, J.M. Temporomandibular disorders, headaches and chronic pain. J. Pain Palliat. Care Pharm.2015; 29: 61–63. [CrossRef] [PubMed]

2. Conti, P.C., Pinto-Fiamengui, L.M., Cunha, C.O., Conti, A.C. Orofacial pain and temporomandibular disorders: The impact on oral health and quality of life. Braz. Oral Res. 2012; 26: 120–123. [CrossRef] PubMed]

3. Zwiri, Abdalwhab, Al-Hatamleh, Mohammad A. I., W. Ahmad, Wan Muhamad Amir, Ahmed Asif, Jawaad, Khoo, Suan Phaik, Husein, Adam, Ab-Ghani, Zuryati, Kassim, Nur Karyatee . Biomarkers for Temporomandibular Disorders: Current Status and Future Directions. Diagnostics 2020; 10(5): 1-18.

4. Ok, S.M.; Lee, S.M., Park, H.R., Jeong, S.H., Ko, C.C., Kim, Y.I. 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: 366–372. [CrossRef] [PubMed]

5. Campos, M.I.G., Campos P.S.F., Line, S.R.P. Inflammatory cytokines activity in temporomandibular joint disorders: A review of literature. Braz. J. Oral Sci. 2006; 5:1054–1062. [CrossRef]

6. Mayank Shrivastava, Ricardo Battaglino, Liang Ye . A comprehensive review on biomarkers associated with painful temporomandibular disorders . International Journal of Oral Science 2021; 13:23 – doi:10.1038/s41368-021-00129-1.

7. Mohammad Khursheed Alam, Mahmud Uz Zaman, Nasser Raqe Alqhtani, Abdullah Saad Alqahtani, Fawaz Alqahtani, Marco Cicciu, Giuseppe Minervini. Salivary Biomarkers and Temporomandibular Disorders: A Systematic Review conducted according to PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. J Oral Rehabil. 2024;51:416–426.

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