The Potency of miRNA 221-3p as a Molecular Biomarker Of Temporomandibular Disoder: Narrative Review

Bimo Rintoko, Ira Tanti**, Endang Winiati Bachtiar***, Boy Muchlis Bachtiar***, Lisa Prihastari *****

**Doctoral Program in Faculty of Dentistry, Universitas Indonesia, Jakarta, Indonesia*
Department of Prosthodontics, Faculty of Dentistry Universitas YARSI, Jakarta, Indonesia
***Department of Prosthodontics, Faculty of Dentistry Universitas Indonesia, Jakarta, Indonesia*
****Department of Oral Biology, Faculty of Dentistry Universitas Indonesia, Jakarta, Indonesia*
*****Department of Dental Public Health, Faculty of Dentistry Universitas YARSI, Jakarta, Indonesia*

Correspondence: lisaprihastari@gmail.com

Received 1 July 2025; 1st revision 16 December 2024;2nd revision 29 December 2025; Accepted 30 December 2025; Published online 31 December 2025

Keywords:
miRNA 221-3p, TMD, genetic, biomarker

ABSTRACT

Background: *Orofacial pain costs more than 32 billion dollars yearly in the United States. The trigeminal nerve might be the source of orof facial pain. Pain can be difficult to diagnose and treat due to the variability of pain complaints. miRNA 221-3p could be a potential biomarker for pain. Genetic polymorphisms and genetic mutations can lead to changes in the activity of inflammatory mediators, sex hormones, matrix-degrading enzymes, and the immune system, which affect bone remodeling homeostasis in the temporomandibular joint.*
Method: *Scientific databases PubMed, Scopus, and Google Scholar were searched for articles published between 2013 and 2023 in order to conduct the study. 168 carefully selected publications providing information on possible biomarkers, particularly miRNA 221-3p, were included in the review of the literature. This study aimed to review and analyze the role of genetic polymorphisms and genetic mutations, particularly miRNA-221-3p, as potential biomarkers in the pathogenesis, diagnosis, and pain mechanisms of temporomandibular disorders (TMD)*
Result: *Genetic polymorphisms and genetic mutations can lead to changes in the activity of inflammatory mediators, sex hormones, matrix-degrading enzymes, and the immune system, which affect bone remodeling homeostasis in the temporomandibular joint. In addition, activity changes were also observed in neurotransmitters and pain receptors, which resulted in relatively high pain sensitivity. Thus, this condition also increases susceptibility to TMD. Genetic analysis and biomarkers of temporomandibular disorders may improve sensitivity and specificity measures in diagnosing and treating patients with TMD*
Conclusion:
As a multifactorial disease, genetic factors are risk factors for TMD. Genetic polymorphisms and genetic mutations can lead to changes in the activity of inflammatory mediators, sex hormones, matrix-degrading enzymes, and the immune system, which affect bone remodeling homeostasis in the TMD.

doi: http://dx.doi.org/10.30659/odj.12.241-250
2460-4119 / 2354-5992 ©2025 National Research and Innovation Agency
This is an open access article under the CC BY-SA license (https://creativecommons.org/licenses/by-sa/4.0/)
Odonto : Dental Journal accredited as **Sinta 3 Journal** (https://sinta.kemdikbud.go.id/journals/profile/3200)
How to Cite: Rintoko, *et all*. The Potency of miRNA 221-3p as a Molecular Biomarker Of Temporomandibular Disoder: Narrative Review. Odonto: Dental Journal, v.12, n.3, p.241-250, December 2025

INTRODUCTION

The orofacial area is composed of heterogeneous hard and soft tissues, it's difficult to make diagnosing and treating pain. Numerous cranial structures, particularly the trigeminal nerve, might be the source of orofacial pain. The majority of the orofacial structures send impulses to the brain via the trigeminal nerve, where they interact dynamically to create a subjective experience of pain that includes cognitive, emotional, and sensory components. Orofacial pain affects individuals in multiple ways, including physically, emotionally, and negatively impacts their quality of life. Orofacial pain-related illnesses can be roughly categorized as odontogenic, musculoskeletal, neurogenic, psychological, headache, and other conditions. Clinically, it can be challenging to distinguish between the many orofacial pain syndromes due to the variability of pain complaints, which can result in incorrect diagnoses, delayed diagnoses, or inefficient treatments. When the pain persists and has no physical or structural explanation, it is more challenging for doctors to treat the patient [1].

Self-reported orofacial pain costs more than 32 billion dollars yearly in the United States, according to cross-sectional population-based studies[2]. Other risk factors mentioned include low socioeconomic level, smoking, psychological issues, and other chronic pain illnesses, with women being more affected by the 2:1 ratio.[3] Clinically speaking, there are two categories for orofacial pain conditions: acute and chronic. The term "chronicity" is typically used differently by researchers and medical practitioners. According to the International Association for the Study of Pain (IASP), "chronic" refers to pain that lasts longer than the average amount of time for recovery; nevertheless, in clinical practice, it must last for at least three months, and for research purposes, it must persist for at least six months[4].

Acute pain has a known origin, is adaptable, reversible, and involves the activation of nociceptors and chemical mediators. Although it can be rather severe and frequently comes with concern and anxiety, a cause is typically established, and treatment is typically successful. However, due to neuroplastic changes in the structure of the central and peripheral nerve systems, chronic pain persists and is resistant to treatment. Chronic pain is a major cause of suffering since it interferes with daily activities and is often accompanied by worry, hopelessness, weariness, depression, and addiction. Its prevalence is currently rising as a result of changing work demands and increased awareness of symptoms. Temporomandibular disorder (TMD) is one of the chronic pain conditions that is a global health issue. Temporomandibular disorders (TMD) are complex and multifactorial conditions characterized by pain in the temporomandibular joint, masticatory muscles, and associated structures. Previous studies have suggested that, in addition to mechanical and psychosocial factors, genetic factors play a significant role in the development and progression of TMD.[2] Genetic polymorphisms and mutations have been shown to influence inflammatory mediators, sex hormones, matrix-degrading enzymes, and immune system responses, thereby disrupting bone remodeling homeostasis within the temporomandibular joint. Furthermore, alterations in neurotransmitters and pain receptor activity have been associated with increased pain sensitivity and susceptibility to chronic orofacial pain.[5,6,7] Recent research has highlighted microRNAs, particularly miRNA-221-3p, as potential biomarkers due to their regulatory role in gene expression and involvement in inflammatory and pain pathways. Understanding these genetic and molecular mechanisms may improve the sensitivity and specificity of TMD diagnosis and contribute to the development of more targeted and effective treatment strategies. This review aimed to investigate genetic polymorphisms, with a focus on miRNA-221-3p, as potential biomarkers to improve the diagnosis and understanding of pain mechanisms in temporomandibular disorders[1]

RESEARCH METHOD

Scientific databases PubMed, Scopus, and Google Scholar were searched for articles published between 2013 and 2023 in order to conduct the study. 168 carefully selected publications providing information on possible biomarkers, particularly miRNA 221-3p, were included in the review of the literature. The aforementioned requirements must be met in order for the manuscript to be considered for the review. The following keywords were used to create a comprehensive list of references: miRNA, miRNA221-3p, TMD, pain, and TMJ diseases. Inclusion Criteria: Studies investigating temporomandibular disorders (TMD) or orofacial pain, Studies examining genetic polymorphisms, genetic mutations, or microRNAs, particularly miRNA-221-3p, in relation to TMD or pain mechanisms, Original research articles, including observational studies (cross-sectional, case–control, cohort) and experimental studies, Studies published in peer-reviewed journals between 2013 and 2023, Articles published in English, Studies conducted in human subjects. Exclusion Criteria: Studies not related to temporomandibular disorders or orofacial pain, Articles that did not evaluate genetic factors, biomarkers, or molecular mechanisms relevant to TMD, Case reports, expert opinions, editorials, letters to the editor, and conference abstracts without full text, Animal studies or in vitro studies not directly applicable to human TMD, Articles published in languages other than English, Studies with insufficient data or unclear methodology

RESULTS AND DISCUSSION

Potential biomarkers

A potential diagnostic technique that has grown greatly in recent years is the use of biomarker tests. A biomarker is an objectively measurable, specified property that represents a healthy biological process, a diseased process, or a biological reaction to a therapeutic intervention, according to the US Food and Drug Administration (FDA). To predict the initial onset, persistence, severity, and prognosis of patient pain, biomarkers are chemically stable substances that are simple to quantify in patients.

Pain biomarkers have been categorized using a variety of techniques. Additionally, researchers have categorized pain biomarkers according to the methods used to collect them, including sampling, genetic testing, imaging, and direct physiological measurements. In general, biospecimens like tissue biopsies and biofluids including plasma, saliva, synovial fluid, and cerebrospinal fluid are used to assess molecular biomarkers. Blood serum used to be the benchmark for assessing and validating biomarkers. Researchers and doctors have become interested in saliva and synovial fluid recently due to the non-invasive collection of saliva and the apparent tissue specificity of synovial fluid. Large molecules are inherently prevented from passing through the synovial membrane, a semi-permeable barrier that surrounds joints. This results in the absence of some joint-specific biochemical indicators in the blood. As a result, individual synovial fluid analyses can reveal joint health and provide real-time information about joints that are unavailable from analyzing serum and saliva.[5]

The role of miRNA

We started the discussion with a group of short RNAs performing RNAi or RNAi interference. Here, short single-stranded RNAs (20-30 nucleotides) act as guide RNAs that rearrange and selectively associate, by base pairing, with other RNAs in the cell. When the target may be a develop mRNA, the little noncoding RNAs can restrain its interpretation or indeed catalyze its pulverization. On the off chance that the target RNA particle

is within the handle of being interpreted, the little noncoding RNA can tie to it and coordinate the arrangement of certain sorts of severe chromatin on its connected DNA layout (Figure 1). The following text describes the functioning of three classes of small noncoding RNAs in a professional manner: microRNAs (miRNAs), small interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs). While the production of these short single-stranded RNA molecules varies, all three types of short RNAs identify their targets through RNA-RNA base pairing and typically result in a reduction in gene expression [8]

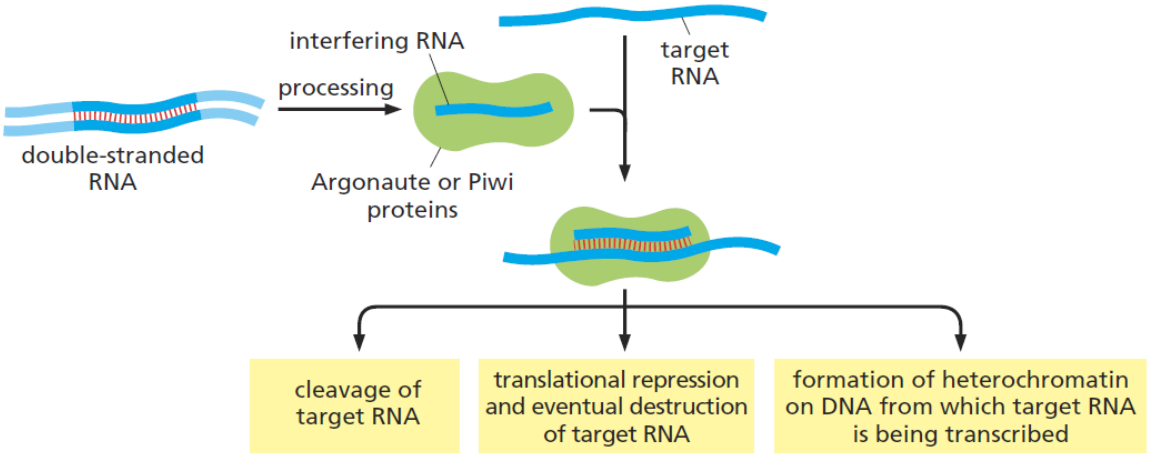

Figure 1. RNA interference in eukaryotes. Single-stranded interfering RNAs are generated from double-stranded RNA. They locate target RNAs through base-pairing and, at this point, several fates are possible, as shown. As described in the text, there are several types of RNA interference; the way the double-stranded RNA is produced and processed and the ultimate fate of the target RNA depends on the particular system. (8)

miRNAs Regulate mRNA Translation and Stability

Over 1,000 distinct microRNAs (miRNAs) are produced from the human genome, and evidence suggests that they play a role in controlling a minimum of one-third of all human protein-coding genes. After being generated, microRNA (miRNA) bases form specific bonds with particular messenger RNAs (mRNAs), thereby precisely regulating their translation and stability. MiRNA precursors are produced through the action of RNA polymerase II and undergo capping and polyadenylation. Next, miRNAs (usually 23 nucleotides long) assemble with a series of proteins and undergo a specialized type of processing to form the RNA-induced silencing complex (RISC). Once RISC is formed, it searches the target mRNA for complementary nucleotide sequences. (Figure 2).

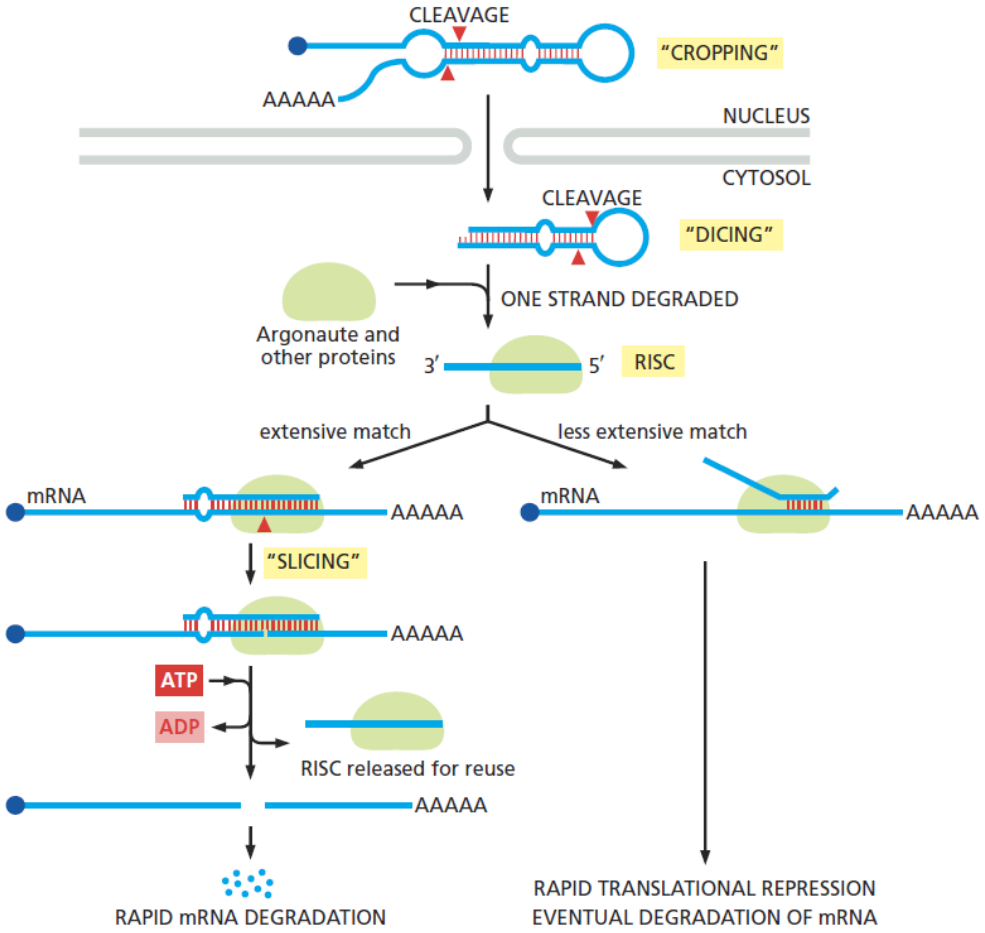

Figure 2. miRNA processing and mechanism of action. The precursor miRNA, through complementarity between one part of its sequence and another, forms a double-stranded structure. This RNA is cropped while still in the nucleus and then exported to the cytosol, where it is further cleaved by the Dicer enzyme to form the miRNA proper. Argonaute, in conjunction with other components of RISC, initially associates with both strands of the miRNA and then cleaves and discards one of them. The other strand guides RISC to specific mRNAs through base-pairing. If the RNA–RNA match is extensive, as is commonly seen in plants, Argonaute cleaves the target mRNA, causing its rapid degradation. In mammals, the miRNA–mRNA match often does not extend beyond a short seven-nucleotide "seed" region near the 5' end of the miRNA. This less extensive base-pairing leads to inhibition of translation, mRNA destabilization, and transfer of the mRNA to P-bodies, where it is eventually degraded. (7)

MiRNAs are tiny RNA molecules that are naturally present within an organism. These molecules are single-stranded and do not encode proteins. Ranging from 18 to 25 nucleotides in length, MiRNAs have the ability to bind to specific regions on messenger RNA molecules, which are responsible for coding proteins. By doing so, MiRNAs can effectively control the expression of target genes[10] Approximately 1500 humans miRNAs[11] Approximately 3% of the identified genes within the human genome are composed of microRNAs. These microRNAs have the ability to control up to 30% of all genes in the human body.[12]

Every microRNA (miRNA) has the ability to control the expression of multiple target genes, which are responsible for producing several proteins. Similarly, individual target genes, which produce specific proteins, can also be regulated by multiple miRNAs.[13]. In this process of miRNA-mRNA interaction, fully developed miRNAs are integrated into the RNA-induced silencing complex (RISC).[9] The binding of this molecule to the 3′ untranslated region (3′-UTR) of target mRNAs (proteins) plays a crucial role in regulating their expression. This process is involved in various physiological and pathological processes, including cell proliferation, development, cytology,

differentiation, apoptosis, autophagy, growth control, stress response, migration, survival, immune response, as well as tumorigenesis, angiogenesis, and metastasis.[13, 14]. The obstruction of these regulatory targets results in a decrease in translation efficiency and/or a decrease in mRNA levels.[15]. MicroRNAs (miRNAs) have the ability to modulate the expression levels of oncogenes and tumor suppressor genes, thereby impacting the progression of cancer. Additionally, miRNAs can directly function as either oncogenes or tumor suppressor genes during the development of cancerous tumors.[16] Consequently, the diminished expression of miRNAs has been demonstrated to play a role in the development of oral squamous cell carcinoma.[17]. MicroRNAs (miRNAs) demonstrate notable stability in both saliva and tissue samples, providing a significant advantage over alternative biomarkers. Research has demonstrated that the analysis of microRNA profiles has the ability to differentiate between healthy oral tissue and cancerous tissue, as well as distinguish various types of tumors, and forecast treatment outcomes or responses[18,19]

microRNA (miRNA)

The epigenetics of chronic pain is a topic that has drawn the interest of numerous researchers in their quest to comprehend the chronicity of pain. In numerous experimental models and clinical pain syndromes, small non-coding inhibitory RNA-class microRNAs (miRNAs) have been found to have a significant role in controlling how pain is processed. A novel class of single-stranded, non-coding RNAs called miRNAs has 19–24 nucleotides and is capable of post-transcriptionally controlling a significant portion of the genome[20]. The 3' end of the miRNA sequence, which is a component of the untranslated region (UTR), or occasionally the 5'UTR end, is where it (miRNA) interacts. This enables a single miRNA to inhibit several gene activities[21].

miRNA221-3p

MiRNA profiles have been described as indicators of TMD events in numerous articles to date. In one study, osteoarthritis patients' synovial fibroblasts showed decreased miRNA221-3p expression. Ets-1, the transcription factor of the first matrix metalloproteinase (MMP) enzyme in charge of tissue damage and articular cartilage remodeling, is discovered to be inhibited by miRNA221-3p, according to research [22] MiRNA 140-5p, which is expressed in TMJ degenerative joint disease (DJD), was examined in a different study. They hypothesized that miR-140-5p might have an impact on the maintenance of mandibular articular cartilage homeostasis and function as a novel predictor of degenerative TMJ alterations. The biological role of microribonucleic acid 101a-3p (miR-101a-3p) and miR21-5p (MiR21) in degenerative TMJ alterations has been examined in a number of other research[23] Researchers hypothesized that miR-101a-3p and miR21-5p have a role in the degeneration of cartilage matrix and TMJ degenerative alterations.[24]. The temporomandibular joint is simpler to approach because it is a surface structure. Comparatively to collecting CSF analogs or trigeminal nerve biopsies, the potential of obtaining salivary, synovial, or even muscle samples to examine TMD biomarkers is more exciting. Because of this, studies investigating molecular biomarkers for TMD can use a variety of body tissues, including blood to biopsies.[25] Patients with TMD were shown to have higher levels of the pro-inflammatory cytokine tumor necrosis factor (TNF) in their synovial fluid[26,27,28,29] and more TMD discomfort is related to higher synovial TNF- levels.[30] A correlation between synovial TNF- levels and intra-articular glucocorticoid injection response has also been observed (Fredriksson et al, 2006) and surgery on the temporomandibular joint[31] following TNF-, with the degree of analgesia matching to a drop in TNF. The pro-inflammatory cytokine interleukin-1 (IL-1) and the mixed-effect

cytokine IL-6 are two more cytokines investigated in TMD. Similar to TNF-, people with TMD have higher levels of IL-1 in their synovial fluid[29,31,] and elevated synovial IL-1 is linked to elevated TMD pain.[27,32] The synovium of TMD patients also contains IL-6 more frequently than that of healthy controls, and higher levels are associated with worsening pain and other TMD symptoms[29,33,34,35,36] TMD has also been examined using salivary biomarkers, intramuscular cytokines, and synovial fluid. Patients with myalgic TMD had higher levels of IL-6, IL-7, IL-8, and IL-13 in their masticatory muscles[37] and the oxidative stress indicators malondialdehyde, 8-hydroxydeoxyguanosine, and antioxidants in saliva.

TMD detection method and the potential of miRNA221-3p as biomarker of TMD

The recently suggested Axis I protocol, known as Diagnostic Criteria for Temporomandibular Disorder (DC/TMD), incorporates verified screening criteria to identify temporomandibular disorders related to pain, as well as the most prevalent ones. This protocol encompasses reliable diagnostic criteria to differentiate between different diseases (with a sensitivity of at least 0. 6 and a specificity of at least 0. 8) and intra-articular disease (with a sensitivity of 0. 0 and a specificity of 0. 7). The diagnostic criteria for various other frequently occurring intra-articular diseases are not comprehensive enough to establish a clinical diagnosis. Nevertheless, they can still be employed for the purpose of initial screening. The inter-rater reliability of clinical assessments linked to validated DC/TMD criteria for pain-related temporomandibular disorders is exceptional (κappa (k) ≥ 0. 5). Additionally, we are pleased to introduce a comprehensive classification system that encompasses a wide range of TMJ disorders, including both frequently encountered and less prevalent conditions. The Axis II protocol incorporates certain original RDC/TMD screening tools while also introducing new tools to evaluate jaw function, behavior, and other psychosocial factors. The Axis II protocol consists of two sets of tools: a screening toolset and a comprehensive self-reporting toolset. The screening instrument consisted of 41 questions that were designed to evaluate various aspects of the individual's pain experience. These included assessing the intensity of the pain, any disturbances caused by the pain, psychological distress, jaw dysfunction, and subfunctional behavior. Additionally, pain plots were utilized to determine the specific location of the pain. The comprehensive tool comprises 81 questions that thoroughly assess jaw function limitations, psychological stress, the presence of additional fear structures, and comorbid pain. It documents these aspects in detail. The newly proposed DC/TMD protocol, based on evidence, is appropriate for utilization in both clinical and research environments.[38]

There is an increasing body of evidence indicating the significant involvement of miRNAs in the regulation of the inflammatory response.[38] More than 25 microRNAs (miRNAs) have been identified as having differential expression in inflamed joints, and they are functionally linked to the degeneration of the joints.[39] MiRNA18a, an RNA molecule that is increased in rheumatoid arthritis synovial fibroblasts, enhances the process of cartilage degradation and contributes to the persistence of chronic inflammation within the affected joint.[40]

MiRNA203 has been documented to increase the expression of nitric oxide (NO) by targeting transient receptor potential vanilloid 4 (TRPV4) in chondrocytes of temporomandibular joint osteoarthritis (TMJOA) cartilage.[41] In our study, we utilized miRNA microarray analysis to examine the expression profile of miRNAs in normal and TMJOA synovial fibroblasts. The results revealed notable differences in the expression of 14 miRNAs, with eight being up-regulated and six being down-regulated. Among these, miRNA221-3p exhibited the most significant down-regulation in TMJOA. To the best of our knowledge, this is the first study to identify the abnormal expression of miRNA221-3p in synovial fibroblasts from individuals with Temporomandibular Joint Osteoarthritis

(TMJOA)/TMD.[22] MiRNA221-3p is a versatile factor expressed in various cell types. Previous studies have reported its role as an anti-angiogenic factor, suppressing vessel formation and migration of endothelial cells in atherosclerosis.[42] MiRNA221-3p has been shown to regulate proliferative signaling pathways, prevent cellular death through autophagy and apoptosis, monitor angiogenesis, and facilitate epithelial-mesenchymal transition in cancer cells[42] Furthermore, it has been observed that an increased level of miRNA221-3p leads to the development of a poorly differentiated, mesenchymal-like phenotype in epithelial cells.[44]

According to the miRanda and TargetScanS algorithms, it has been predicted that Ets-1 may be a target of miRNA221-3p. Ets-1 is a key transcription factor within the its family, and it is expressed in a variety of cell types, including B cells, endothelial cells, fibroblasts, and neoplastic cells. Additionally, it has been previously observed that the aforementioned can also be detected in fibro-cartilaginous cells of the temporomandibular joint (TMJ). (45) Recent reports have indicated that miRNA221-3p specifically targets Ets-1, thereby playing a role in the vascular inflammatory response observed in certain diseases, including obesity and atherosclerosis[46] Our investigation focused on determining whether miRNA221-3p has the ability to regulate the expression of Ets-1 in synovial fibroblasts associated with temporomandibular joint osteoarthritis (TMJOA). Through the use of gain and loss expression techniques, we were able to demonstrate the impact of miRNA221-3p on the expression of Ets-1 in TMJOA synovial fibroblasts. Additionally, our dual luciferase reporter assay provided evidence suggesting that miRNA221-3p suppresses Ets-1 expression by directly binding to its 30-UTR region. It is worth noting that even after introducing miRNA221 mimics through transfection, cells genetically modified with a plasmid containing the Ets-1 30-UTR region still exhibited luciferase activity. This observation can be attributed to the high sensitivity of the luciferase reporter assay kit, and the remaining luciferase value represented the background signal.[22]

In the current study, it was observed that IL-1b had a time and dose-dependent effect on reducing the expression of miRNA221-3p in synovial fibroblasts associated with TMJOA. Conversely, the expression of Ets-1 was increased. These results suggest that the presence of a significant amount of IL-1b in TMJOA contributes to the abnormal expression of miRNA221-3p in synovial fibroblasts. Furthermore, it was also discovered that TNF-a has a suppressive effect on the expression of miRNA221-3p in TMJOA synovial fibroblasts. Further investigation is currently underway to explore this finding.[22]

The decrease of miRNA221-3p in synovial fibroblasts, caused by the high levels of IL-1b in an inflamed environment, triggers an increase in Ets-1 expression. This, in turn, activates the secretion of MMP1, MMP9, MCP-1, and IL-8, resulting in the ongoing pathological progression of TMJOA. Consequently, miRNA221-3p, which is known to have a protective role in the joints, holds great potential as a molecular target for the treatment of TMJOA.[22] This study has several limitations, including heterogeneity among included studies and the lack of clear integration between previous research findings and the objectives of the literature review. This study was not conducted as a systematic review or meta-analysis; therefore, the findings have not been quantitatively synthesized and cannot be objectively measured

CONCLUSION

As a multifactorial disease, genetic factors are risk factors for TMD. Genetic polymorphisms and genetic mutations can lead to changes in the activity of inflammatory mediators, sex hormones, matrix-degrading enzymes, and the immune system, which affect bone remodeling homeostasis in the temporomandibular joint. In addition, activity changes were also observed in neurotransmitters and pain receptors, which resulted in relatively high pain

sensitivity. Thus, this condition also increases susceptibility to TMD. Genetic analysis and biomarkers of temporomandibular disorders may improve sensitivity and specificity measures in diagnosing and treating patients with TMD. Among potential biomarkers, miRNA-221-3p shows promise in understanding pain mechanisms and disease susceptibility in TMD. However, as this study was not conducted as a systematic review or meta-analysis, the findings could not be quantitatively synthesized, and the conclusions should be interpreted with caution. Further well-designed systematic reviews and meta-analyses are needed to objectively evaluate the role of genetic biomarkers in the diagnosis and management of temporomandibular disorders.

ACKNOWLEDGEMENT

All the authors would like to acknowledge all lecturer and staff at Universitas Indonesia and Universitas YARSI to conduct this review article.

REFERENCES

1. M. Shrivastava, R. Battaglino, and L. Ye, “A comprehensive review on biomarkers associated with painful temporomandibular disorders,” Int. J. Oral Sci., vol. 13, 2021.
2. A. Lövgren, B. Häggman-Henrikson, C. M. Visscher, F. Lobbezoo, S. Marklund, and A. Wänman, “Temporomandibular pain and jaw dysfunction at different ages covering the lifespan: A population-based study,” Eur. J. Pain, vol. 20, no. 4, pp. 532–540, 2016.
3. P. Svensson and A. Kumar, “Assessment of risk factors for orofacial pain and recent developments in classification: Implications for management,” J. Oral Rehabil., vol. 43, no. 12, pp. 977–989, 2016.
4. H. Merskey and N. Bogduk, Classification of Chronic Pain, 2nd ed. Seattle, WA, USA: IASP Press, 1994.
5. A. Velly, Orofacial Pain Biomarkers. 2017.
6. Latief and Shofiyah et al., “Enhancing diagnostic precision: The role of specialized head coil MRI in disc displacement diagnosis of temporomandibular joint,” Odonto: Dental Journal, vol. 12, no. 2, pp. 208–221, 2025.
7. Y. Rahmad, E. Edrizal, and A. T. O. Berhana, “The relationship between stress and temporomandibular disorder in students of the Faculty of Dentistry, Baiturrahmah University class of 2020,” Odonto: Dental Journal, vol. 11, no. 1, pp. 105–114, 2024.
8. S. Bustin, “Molecular biology of the cell, sixth edition,” Int. J. Mol. Sci., vol. 16, no. 12, pp. 28123–28125, 2015.
9. V. Gassling et al., “Disease-associated miRNA–mRNA networks in oral lichen planus,” PLoS One, vol. 8, no. 5, 2013.
10. H.-C. Chen et al., “Genetic variants in microRNA-146a and microRNA-1269b are associated with decreased risk of oral premalignant lesions and cancer,” Arch. Oral Biol., vol. 72, pp. 21–32, 2016.
11. S. Jonas and E. Izaurralde, “Towards a molecular understanding of microRNA-mediated gene silencing,” Nat. Rev. Genet., vol. 16, no. 7, pp. 421–433, 2015.
12. E. Nylander et al., “Changes in miRNA expression in sera and correlation with disease duration in multifocal mucosal lichen planus,” J. Oral Pathol. Med., vol. 41, no. 1, pp. 86–89, 2012.
13. E. Chattopadhyay et al., “Expression deregulation of miR-31 and CXCL12 in oral precancers and cancer,” Sci. Rep., vol. 6, 2016.
14. J. Wang et al., “miR-125b inhibits keratinocyte proliferation and promotes apoptosis in oral lichen planus,” Biomed. Pharmacother., vol. 80, pp. 373–380, 2016.
15. H. Guo et al., “Mammalian microRNAs predominantly act to decrease target mRNA levels,” Nature, vol. 466, no. 7308, pp. 835–840, 2010.
16. Y. Hou et al., “Association between miR-499a polymorphism and oral squamous cell carcinoma progression,” Oral Dis., vol. 21, no. 2, pp. 195–206, 2015.
17. N. Lin et al., “MicroRNAs as diagnostic biomarkers in oral carcinoma: A meta-analysis,” Clin. Lab., vol. 62, 2016.
18. K. F. Hung et al., “MicroRNA-31 upregulation predicts increased risk of progression of oral potentially malignant disorder,” Oral Oncol., vol. 53, pp. 42–47, 2016.
19. G. Zhu et al., “Identification of gene and microRNA signatures for oral cancer developed from oral leukoplakia,” Biomed Res. Int., vol. 2015, 2015.

20. H. H. Andersen, M. Duroux, and P. Gazerani, “MicroRNAs as modulators and biomarkers of inflammatory and neuropathic pain,” Neurobiol. Dis., vol. 71, pp. 159–168, 2014.
21. M. J. López-González, M. Landry, and A. Favereaux, “MicroRNA and chronic pain: From mechanisms to therapeutic potential,” Pharmacol. Ther., vol. 180, pp. 1–15, 2017.
22. J. Xu et al., “MicroRNA-221-3p modulates Ets-1 expression in synovial fibroblasts from TMJ osteoarthritis patients,” Osteoarthritis Cartilage, vol. 24, no. 11, pp. 2003–2011, 2016.
23. D. Mao et al., “MicroRNA-101a-3p in TMJ osteoarthritis pathogenesis,” J. Oral Pathol. Med., vol. 50, no. 2, pp. 236–243, 2021.
24. A. Zhang et al., “Knockout of miR-21-5p alleviates cartilage degradation in TMJ osteoarthritis,” Bone Joint Res., vol. 9, no. 10, pp. 689–700, 2020.
25. T. L. Doshi et al., “Biomarkers in temporomandibular disorder and trigeminal neuralgia,” Can. J. Pain, vol. 4, no. 1, pp. 1–18, 2020.
26. K. Fu et al., “Tumor necrosis factor in synovial fluid of TMD patients,” J. Oral Maxillofac. Surg., vol. 53, no. 4, pp. 424–426, 1995.
27. T. Takahashi et al., “Proinflammatory cytokines in synovial fluids of TMD patients,” Oral Surg. Oral Med. Oral Pathol., vol. 85, no. 2, pp. 135–141, 1998.
28. R. Emshoff et al., “TMJ pain and synovial fluid TNF-α levels,” Oral Surg. Oral Med. Oral Pathol., vol. 90, no. 4, pp. 442–449, 2000.
29. K. Kaneyama et al., “Analysis of cytokines in synovial fluid of TMJ disorders,” Oral Surg. Oral Med. Oral Pathol., vol. 99, no. 3, pp. 276–284, 2005.
30. S. Nordahl, P. Alstergren, and S. Kopp, “TNF-α in synovial fluid and plasma in TMJ pain,” J. Oral Maxillofac. Surg., vol. 58, no. 5, pp. 525–530, 2000.
31. D. M. Shafer et al., “TNF-α as a biochemical marker of pain in TMJ,” J. Oral Maxillofac. Surg., vol. 52, no. 8, pp. 786–791, 1994.
32. T. Suzuki et al., “IL-1β expression in TMJ internal derangement,” Oral Surg. Oral Med. Oral Pathol., vol. 88, no. 4, pp. 413–417, 1999.
33. E. Kubota et al., “Synovial fluid cytokines and proteinases as markers of TMJ disease,” J. Oral Maxillofac. Surg., vol. 56, no. 2, pp. 192–198, 1998.
34. C. Shinoda and S. Takaku, “Cytokines and TIMP-1 in TMJ synovial fluid,” Oral Dis., vol. 6, no. 6, pp. 383–390, 2000.
35. M. Nishimura et al., “Proinflammatory cytokines and arthroscopic findings in TMJ,” Br. J. Oral Maxillofac. Surg., vol. 40, no. 1, pp. 68–71, 2002.
36. J. Sato et al., “IL-6 expression in synovial tissues of TMJ patients,” Br. J. Oral Maxillofac. Surg., vol. 41, no. 2, pp. 95–101, 2003.
37. S. Louca Jounger et al., “Increased intramuscular cytokines in jaw muscle pain,” J. Headache Pain, vol. 18, no. 1, 2017.
38. E. Schiffman et al., “Diagnostic criteria for temporomandibular disorders (DC/TMD),” J. Oral Facial Pain Headache, vol. 28, no. 1, pp. 6–27, 2014.
39. C. Wu et al., “MicroRNAs in chondrogenesis and osteoarthritis,” Int. J. Mol. Med., vol. 34, no. 1, pp. 13–23, 2014.
40. M. Trenkmann et al., “TNF-α-induced microRNA-18a activates synovial fibroblasts,” Arthritis Rheum., vol. 65, no. 4, pp. 916–927, 2013.
41. F. Hu, W. Zhu, and L. Wang, “MicroRNA-203 regulates nitric oxide in TMJ chondrocytes,” Arch. Oral Biol., vol. 58, no. 2, pp. 192–199, 2013.
42. B. Qin et al., “MicroRNA-221/222 regulate ox-LDL-induced endothelial apoptosis,” Mol. Cell. Biochem., vol. 405, pp. 115–124, 2015.
43. W.-X. Chen et al., “miR-221/222 as biomarkers for breast cancer,” Tumor Biol., vol. 34, no. 3, pp. 1361–1370, 2013.
44. E. N. Howe, D. R. Cochrane, and J. K. Richer, “The miR-200 and miR-221/222 families,” J. Mammary Gland Biol. Neoplasia, vol. 17, no. 1, pp. 65–77, 2012.
45. S. Kapila, Y. Xie, and W. Wang, “Induction of MMP-1 by relaxin,” Orthod. Craniofac. Res., vol. 12, no. 3, pp. 178–186, 2009.
46. Meerson et al., “Human adipose microRNA-221 in obesity,” Diabetologia, vol. 56, no. 9, pp. 1971–1979, 2013.