

REVIEW

Role of female reproductive hormones and genetics in temporomandibular joint disorders

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ABSTRACT

The disorders of temporomandibular joint manifest clinically with disruptions in its movement and facial pain. Women exhibit a three-fold higher propensity for developing temporomandibular joint disorders compared to men. There are several studies describing the effects of female reproductive hormones on temporomandibular joint structures and pain perception, shedding light on the genetic influence underlying these conditions. Several polymorphisms have been studied and documented in the literature, shedding light on the genetic background of temporomandibular joint disorders.

This review aims to propose a novel approach to the complex diagnosis and treatment of this type of disorders. Specifically, we advocate for heightening the emphasis on young women diagnosed with temporomandibular joint disorders during their reproductive years, as such manifestation could potentially serve as early indicators of other underlying health conditions linked to the reproductive system. We posit that genetic studies hold promise as a cornerstone for tailoring personalized treatment strategies for TMJD in the future (*Tab. 1, Ref. 46*). Text in PDF www.elis.sk

KEY WORDS: temporomandibular joint disorders, infertility, female reproductive hormones, genetic polymorphism.

Introduction

The temporomandibular joint (TMJ) is a synovial joint facilitating the mandibular motion. Disorders of this joint encompass a spectrum of symptoms not only pertaining to the joint itself, but also extending to the surrounding masticatory muscles and supporting structures of the joint. These disorders clinically manifest with facial pain and alterations in joint movement, often accompanied by aberrant pathological sounds (1, 2, 3).

The etiology of the development of TMJ disorder (TMJD) is multifactorial, involving physical, functional and psychological factors (4).

Compared to men, women exhibit a three-fold higher susceptibility to developing temporomandibular joint disorders such as TMJ disc displacement (malposition of the disc in relation to the mandibular condyle and articular eminence (5)) and arthralgia (6, 7, 8). This level of prevalence can stem from specific characteristics

unique to the female population, including greater intraarticular pressure and joint laxity, smaller joint space and higher levels of TMJ pain, potentially influenced by estrogen (9). Also, several studies have indicated a higher prevalence of specific mutated genotypes associated with pain, inflammation, and tissue degradation in women (10–13). The TMJD symptoms in women usually start appearing at the onset of puberty while their prevalence decreases after menopause (14, 6). Furthermore, clinical observations indicate a rising prevalence of TMJD among patients across successive decades (15).

There are several possible mechanisms for the development of TMJD proposed in the literature, albeit with conflicting findings (1).

Among these mechanisms, genetics has surfaced as a promising avenue leading to deeper comprehension of TMJD, a pivotal step toward tailoring personalized therapeutic interventions in the future. The published findings of studies exploring the role of genetic polymorphisms may serve as a foundation for elucidating the genetic background of TMJD (4, 11–14, 16–26).

Achieving a comprehensive understanding of the pathophysiology of TMJD holds the key for transitioning from treating clinical symptoms to addressing its underlying causes. This necessitates an in-depth exploration of biological processes in TMJ bone degeneration and cartilage deterioration.

Drawing from these documented findings, our focus revolves around two factors potentially influencing the TMJD development:

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female reproductive hormones and genetics, and the plausible interplay between them.

Role of estrogen in pathogenesis of temporomandibular joint disease

Analysis of existing literature in previous reviews indicates a concerning trend of inconsistency and occasional contradictions among studies investigating the topic of the relationship between TMJD and female reproductive hormones (27). A study conducted by Berger et al. reviewed nine studies focused on the impact of estrogen on TMJD while seven of these studies have confirmed a correlation between estrogen levels and TMJD (28). These findings align with reports implicating a positive correlation between the level of female reproductive hormones and the frequency and onset of TMJD. On the other hand, other studies have proposed a contrasting perspective, indicating that low levels of estrogen may contribute to the severity and frequency of painful sensations associated with TMJD (29–32).

Female reproductive hormones, estrogen and progesterone, circulate in the bloodstream, where they bind with plasma proteins and influence the metabolism of various tissues and organs. Their impact can be both direct and indirect, mediated through nuclear estrogen receptors and receptors present in cell membranes, thereby affecting the gene expression. Genetic variants in the structure of these receptors can contribute to a range of symptoms, including joint inflammation, bone lesions, and pain. Moreover, these hormones can modulate the immunological response peripherally through receptors in the spleen, bone marrow or thymus. Estrogen, in particular, can also regulate the production of inflammatory cytokines when they interact with monocytes and macrophages (33, 34).

In a study conducted by Bi et al, the researchers explored the potential modulation of Nav1.7 (voltage-gated sodium channel) by estradiol in the trigeminal ganglion. Their results suggested that Nav1.7 is critical for perception of pain and is a target for estradiol. Also, they observed that higher expression levels of Nav1.7 in the trigeminal ganglion was associated with increased sensitivity of the temporomandibular joint to mechanical stimuli. The authors posited that the upregulation of Nav1.7 expression induced by estradiol could contribute to the increase in nociception in temporomandibular joints affected by inflammation (35).

The influence of estrogen extends to the limbic system, where it is implicated in heightening the perception of pain and reducing the pain threshold (36, 37).

A deficiency in estrogen is thought to contribute to TMJD development. The restriction of proteoglycans synthesis in the articular cartilage as well as the impaired synthesis of proteins and collagen in the articular disc, can cause structural lesions in the TMJ (27).

Estrogen can modulate degradation of extracellular matrix through the regulation of matrix metalloproteinase (MMPs) expression in various cell types (38). Specifically, β -estradiol is known for its ability to potentiate the induction of MMPs, thereby promoting further degradation of cellular matrix in both reproductive and non-reproductive tissues, including the TMJ (39)

Role of progesterone in pathogenesis of temporomandibular joint disease

Progesterone can negatively affect the expression of Nav1.7 in the trigeminal ganglion through transcription-regulating mechanism initiated by binding of progesterone to PR α or PR β in the nucleus of cells. This reduces neuronal stimulation, thereby suppressing pain sensation associated with inflammation in TMJD (40).

This observation is supported by the findings of Bi et al, who documented the important role of Nav1.7 in the trigeminal ganglion in the development of allodynia in the TMJ affected by inflammation (35).

In a separate study conducted by the same authors, it was observed that progesterone can reversibly affect voltage-gated sodium channel (INa) isolated from neurons of the trigeminal ganglion. Specifically, progesterone was found to reduce peak values of INa, which may result in a higher depolarization threshold, leading to slower activation and subsequent reduction in neuronal excitability. Consequently, progesterone could act as an analgesic by depressing INa activity. However, the precise role of progesterone in modulating INa activity remains incompletely understood (41).

In contrast to the effect of relaxin and estrogen, progesterone suppresses induction of matrix metalloproteinase (MMPs), such as MMP-1, MMP-2, MMP-3 and MMP-9 in reproductive tissues cells (42) as well as MMP-3, MMP-9 and MMP-13, in cells of TMJ tissues in mice, thereby mitigating the matrix loss. Conversely, estrogen and relaxin induce the expression of these MMPs, which subsequently contributes to the degradation of collagen and glycosaminoglycans in TMJ tissues (43).

The study conducted by Kapila et al showed that tissues of the TMJ disc and pubic symphysis exhibited similar expression profiles of the estrogen receptors alpha and beta, relaxin-1 receptor (RXFP1, LGR7), and insulin-like peptide 3 receptor (RXFP2, LGR8). Notably, these profiles differed from those observed in cells from the knee meniscus. Based on these findings, the authors proposed a novel model for targeted tissue transformation of cartilage of specific joints through hormone-mediated induction of select MMPs (43).

Relationship between TMJD and polycystic ovary syndrome

All above-mentioned pathological mechanisms implicated in the development of TMJD bear resemblance to those underlying polycystic ovary syndrome (PCOS) development. In a study conducted by Yazici et al, the incidence of TMJD was investigated in patients with PCOS. The study revealed a startling observation that the incidence of TMJD in these individuals was 7 times higher compared to the control group (44).

Role of oral contraceptives in TMJD

In the OPPERA study published in 2021, a comprehensive investigation involving 1,475 women, the role of hormonal contraceptives was scrutinized. Despite the inherent limitations of this

prospective study, which spanned 2.5 years, compelling evidence emerged linking the use of hormonal contraceptives to symptoms such as headaches, TMJD pain and facial pain. Importantly, a causal relationship between hormonal contraceptives and these symptoms was established. It was postulated that estrogen and its effect on perceiving pain could underlie these adverse effects from hormonal contraceptives. Based on previous results, it is suggested that patients experiencing side effects from hormonal contraceptives containing estrogen should consider estrogen-free alternatives (45).

Role of genetics in TMJD

Genetic factors have been identified as significant contributors to the etiology of TMJD, as highlighted by The American Academy of Orofacial Pain in 2008.

Baratto et al suggested that two pain-related genes, Ankyrin Repeat and Kinase Domain Containing 1 (ANKK1) and Dopamine Receptor D2 (DRD2) might influence TMJD symptoms and signs (4). Research suggests an association between variations in DRD2-mediated neurotransmission in central brain regions and acute pain intensity in response to experimental pain stimuli in humans. (16) Also, genetic polymorphisms of DRD2 have been linked to the vulnerability to chronic pain (17). Both DRD2 and ANKK1 genes are located next to each other on chromosome 11q23.1 and genetic polymorphism on ANKK1 (rs1800497) can reduce dopamine receptor DRD2 expression by 40%, potentially exerting a negative effect on the dopaminergic pathway (4). In a study involving 115 male construction workers, Baratto et al. found a statistical difference in DRD2 rs6276 among patients with chronic pain and

in ANKK1 rs1800497 (4). Dopamine is believed to influence pain in the joint, local sensitivity and reflex activity developed by masticatory muscles (18). Also, polymorphism rs6276 at DRD2 has been related to bruxism in pediatric population, equally to the rs180049 polymorphism in ANKK1 (19).

Several associations have been observed between internal derangements of the TMJ and polymorphism in genes implicated in various biological processes, including degradation of extracellular matrix components (matrix metalloproteinase 1 (MMP1)) (11), sensitivity to pain (catechol-O-methyltransferase (COMT)) (13), anti-inflammation (interleukin 10 (IL10)) (20) and proinflammation (interleukin 6 (IL6), interleukin 1 beta (IL1 β) and tumor necrosis factor alpha (TNF α)) (12, 21, 22).

The presence of 2G allele of the 1607 1G/2G polymorphism of MMP1 may disrupt the balance of matrix metalloproteinases and their inhibitor in the articular disc of TMJ, potentially creating an environment that becomes sensitive to the development of intra-articular disorders. Existing literature has elucidated the connection between rs1799750 polymorphism of MMP1 and simple discopathy of TMJ (TMJ disc displacement with reduction) (11, 23, 24).

IL-10, a cytokine known for its anti-inflammatory effects, functions by downregulating some proinflammatory cytokines such as IL6 and TNF α . The AA genotype of the -1028A/G IL10 SNP was associated with TMJD pain. Leading to reduced secretion of IL10. The GA genotype of the -308G/A TNF α SNP has been associated with chronic TMJ pain, resulting in intermediate secretion of proinflammatory TNF α (25). Furthermore, polymorphisms such as -572C/G IL6 rs1800796 and -597G/A IL6 rs 1800797 may contribute to elevated levels of IL6 (26).

Tab. 1. Effect of estrogen, progesterone, and genetic polymorphism on TMJD development and clinical symptoms.

Target	Hormone	Effect	Result	References
Expression of Nav1.7 in trigeminal ganglion	Estrogen	Positively affects expression	Lowers threshold of pain, causing hyperalgesia	Bi RY et al (35)
	Progesterone	Negatively affects expression	Analgesic effect	Bi RY et al (41)
MMPs that cause degradation of TMJ tissues	Estrogen	Inducing MMPs	Positively affects degradation of matrix in TMJ	Marin-Castano ME et al (38)
	Progesterone	Suppresses induction of MMPs	Negatively affects degradation of matrix in TMJ	Di Nezza LA et al, Kapila S et al (42, 43)
Receptor/gene	Genetic polymorphism	Result	References	
ANKK1	rs18497	Reduce DRD2 receptor – negative effect on dopaminergic pathway	Baratto SSP et al (4)	
DRD 2	rs6276	Connected with bruxism and chronic pain	Baratto SSP et al (4)	
MMP1	1607	Disruption of matrix metalloproteinases and their inhibitors in the articular disc of TMJ	Rosales AS et al, Braga SP et al, Luo S et al (11, 23, 24)	
	rs1799750	Connection with simple discopathy of TMJ	Rosales AS et al, Braga SP et al, Luo S et al (11, 23, 24)	
IL6	-572C/G IL6 rs1800796 -597G/A IL6 rs1800797	Elevation of proinflammatory IL6 levels	Terry CF et al (26)	
IL10	-1802A/G IL10 SNP	Low secretion of anti-inflammatory IL10	Campello CP et al (25)	
TNF α	-308G/A TNF α SNP	Intermediate secretion of proinflammatory TNF α	Campello CP et al (25)	
COMT, 5-HTT	polymorphism	Elevated perception of pain, depression, anxiety	Brancher JA et al (13)	
ESR1	polymorphism	Predisposition to myogenic TMJD	Quinelato V et al (14)	
ESRRB	polymorphism	Predisposition to articular TMJD	Quinelato V et al (14)	

Polymorphisms in genes such as 5-HTT (serotonin transporter, often referred to as “happiness hormone”) and COMT have been linked to increased predisposition towards heightened pain perception, supporting the transition to the chronic phase of pain and enhancing the predisposition to depression and anxiety (13).

Several polymorphisms in genes ESR1 and ESRRB were associated with a higher risk of developing muscle disorders and TMJD. A study by Quinelato, V. et al. identified a connection between polymorphism in the ESR1 gene and myogenic TMJD, while polymorphisms in the ESRRB gene were linked to articular TMJD (14).

Conclusion

In this review we aimed to underscore the significant role of female reproductive hormones in pathological mechanisms of temporomandibular joint disorders and the extent of their clinical symptoms (Tab. 1). Compared to men, women exhibit a three-fold higher propensity to developing temporomandibular joint disorders (6). This elevated prevalence could be attributed, at least in part, to their increased sensitivity and tendency to visit healthcare facilities more often than men (46). It needs to be underscored that the recognition of biological processes underlying the temporomandibular joint bone and cartilage degeneration, particularly the in-depth elucidation of the impact of female reproductive hormones, warrant a further profound investigation.

Another aspect of this work was to describe the role of genetics in the development of TMJD. Numerous studies have attempted to establish connections between specific polymorphism and TMJD, examining both the development of this disorder and its associated symptoms. In this review, we outlined its associations with polymorphisms of ANKK1, DRD2, MMP1, IL6, IL10, TNF α , COMT, 5-HTT, ESR1, and ESRRB (Tab. 1). It is our hope that in the future, a comprehensive understanding of the pathways and connections involved will be achieved, ultimately serving as a foundation for enhancing the diagnostic precision and targeted treatment of patients with TMJD.

We believe that future studies should prioritize investigating the connection between hormonal imbalances, irregularities of the menstrual cycle in women and intraarticular temporomandibular joint disorders.

When we are able to fully comprehend this connection and understand the reason why more women than men experience symptomatic temporomandibular disorders, we can shift our focus toward personalized treatment for these female patients. It is possible that by focusing on the understanding of the pathological mechanisms of these disorders, we may discover new directions for treating TMJD.

Another important finding we wish to emphasize is the increasing number of female patients diagnosed with TMJD with each passing decade. There is also a growing population of female patients experiencing fertility issues and irregularities in the menstrual cycle, significantly affecting their quality of life. The diagnosis is often established belatedly, after the emergence

of severe overall health problems. We propose that women at reproductive age presenting with severe temporomandibular joint disorders should undergo routine dental check-ups for early detection. The subsequent referral to specialists such as maxillofacial surgeons and gynecologists for comprehensive examination of their hormonal profile should be considered. This approach could facilitate early diagnosis and treatment of potential infertility issues and reproductive system diseases or enable the patients to be closely monitored until necessary treatment.

Learning points

- Female reproductive hormones play a role in the development and clinical manifestation of TMJD. The potential effects of hormonal contraceptives should be considered in association with TMJD, and women experiencing exacerbated TMJD symptoms after using of hormonal contraceptives should consider switching to progesterone-only hormonal contraceptives.
- Understanding the pathological mechanism of TMJD and its association with female reproductive hormones can pave the way for future treatment approaches for TMJD.
- If TMJD is diagnosed during a routine dental check-up in women of reproductive age, further examination of their hormonal profile should be considered. This approach enables early diagnosis and potential treatment of reproductive system disease, thereby improving their quality of life.
- Various polymorphisms have been directly or indirectly associated with the development and symptoms of TMJD, with a higher prevalence observed in women for some of these mutations.
- Genetic study may hold the key for personalized treatment approaches for TMJD in the future.

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Received January 15, 2024.

Accepted March 14, 2024.