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Review Article

Relationship Between Temporomandibular Disorders and Fluctuations of Estrogen and Progesterone Levels: Systematic Review

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Abstract

Aim of Investigation: To confirm the relationship between TMD and hormonal levels in young females.

Methods: The authors, including a health sciences librarian, developed a systematic literature review. The databases search included PubMed, Cochrane Database of Systematic Reviews and Cochrane Central Registry of Controlled Trials, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and Web of Science CINAHL. The searches retrieved articles on TMD and hormones with a population focus on adults. Searches included a language limit of English-only results and articles published from 2000 forward. Three individuals screened the results for reliability and to reduce potential bias related to inclusion of results.

Search items: hormones-estrogen-progesterone-TMD-pain-estradiol.

Results: The search yielded 518 results with 438 screened after removal of duplication. Sixty-nine results were screened based upon title and abstract. A total of 10 articles are included in this review.

Summary of the included articles:

- Estrogen levels has no influence on TMD [13].
- Lower progesterone in the luteal phase causing TMD [13].
- Estrogen and progesterone do not impact TMD [14].
- Higher estrogen during the follicular phase led to more pain in TMD [15].
- Higher serum estradiol produces more TMD pain [16].
- TMD pain in women is highest at times of lowest estrogen, but rapid estrogen change may also be associated with increased pain [17].
- Low circulating serum estradiol makes it impossible for the natural reparative capacity of the condyle, leading to condylar lysis [18].
- TMD Pain levels in women were influenced by hormonal fluctuations of the menstrual cycle [19].

Conclusion: This systematic review confirms that fluctuations of estrogen and progesterone levels might be more significant to TMD pain compared to the specific levels of these hormones.

Keywords: *Temporomandibular Disorders (TMD); Estrogen; Progesterone; Estradiol*

Introduction

Temporomandibular Disorders (TMD) is an all-encompassing term that includes several clinical problems involving pain and dysfunction of the masticatory muscles and/or temporomandibular joint [28]. Clicking, popping, or grinding of the jaw, jaw aches, pain with chewing, earaches, neck pain, limited jaw opening, and headaches are among some of the many symptoms. These symptoms can range from mild to debilitating, negatively affecting the quality of life in impacted adults [20]. According to population-based studies, TMD affects approximately 10% to 15%, with only a small fraction of those actively seeking treatment [21]. Some studies have reported higher incidences of TMD in the population, up to 25% [22] and multiple studies indicate up to 33% [23-25]. Over recent decades, it has been found that TMD is more common in females than males [27], with numerous studies deeming the female gender twice as likely to develop TMD symptoms than males [21,26]. Women in their childbearing years account for 90% of all people suffering from TMD. Pain onset tends to occur during reproductive years [13].

With the highest prevalence of TMD in women during their reproductive years, estrogen has been proposed to play a contributory factor in TMD. Previous research has led to different conclusions on the effect hormones, particularly estrogen, have on experiencing TMD symptoms. LeResche., *et al*. studied 126 women, some of whom were using oral contraceptives, and found that TMD pain in women is highest at times of lowest estrogen for both groups [17]. Additionally, LeResche., *et al*. Note that rapid estrogen change may also be associated with increased pain [17]. In opposition, Landi found that higher serum estradiol levels might produce greater stimulation of the TMJ joint, causing increased discomfort [16]. While both authors agree that hormones play a role in the pathophysiology of TMD, other researchers believe estrogen does not affect the joint. Rezaii., *et al*. studied women over their entire menstrual cycle and found no differences in pain sensitivity across any of the 3 phases - early follicular, ovulatory, or mid-luteal [14]. Additionally, Madani., *et al*. concluded that there was no statistical difference in levels of 17B-estradiol, the most potent form, between patients who have TMD and those without TMD [13]. However, Madani., *et al*. found that women experiencing internal derangement of the TMJ had lower levels of progesterone than healthy subjects [13]. With the differing conclusions in literature, we aim to discover what role estrogen has on the TMJ and those that suffer from TMD.

Aim of the Study

This systematic review aims to determine the exact relationship between TMD and estrogen. Although the etiology of TMD is multifactorial, including parafunctional habits, trauma, genetics, stress, and psychosocial factors, we believe the fluctuation of estrogen significantly impacts the development of TMD.

Materials and Methods

The authors, including a health sciences librarian, developed a systematic literature review. The databases search included PubMed, Cochrane Database of Systematic Reviews and Cochrane Central Registry of Controlled Trials, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and Web of Science CINAHL. The searches retrieved articles on TMD and hormones with a population focus on adults. Searches included a language limit of English-only results and articles published from 2000 forward. The initial results yielded 518 citations with the removal of 80 duplicates. Sixty-nine titles and abstracts were screened and a total of 55 articles included for review. Three individuals screened the results for reliability and to reduce potential bias related to inclusion of results. A complete listing of the search terms is available as an supplemental file.

Search items: hormones- estrogen-progesterone-TMD-pain-estradiol.

Results

According to Wang, it is thought that estrogen plays a role in TMJ disease due to the presence of high-affinity estrogen receptors found in many components of the temporomandibular joint [29]. LeResche stated that temporomandibular pain changes across the menstrual cycle, with TMD pain being highest at times of lowest estrogen production [17]. The study also went on to find that not only low levels but also rapid estrogen change may also be associated with increased TMD pain. Gunson had similar overarching results stating that it was, in fact, the low circulating estradiol (a form of estrogen hormone produced by ovaries, breasts, and adrenal glands) that accounts for local

inflammatory factors leading to TMD pain [18]. Contrary to LeResche and Gunson, Madani found no statistical significance between TMD and control groups on mean serum levels of estradiol, but rather the increased serum level of progesterone was significantly higher in the control group than the TMD group, stating that it is the lower levels of progesterone that causes TMD pain [13]. Riberio-Dasilva studied the influence of monocytic hyperinflammatory response on TMD pain and found a correlation between the two [15].

Furthermore, the study concluded that the concentration of estrogen affected the inflammatory response, with low levels of estrogen resulting in increased response. Villanova studied the influence of hormones on pain and mastication on TMD symptoms and found that the lowest pain was observed during the ovulatory phase [19]. Estrogen levels are thought to be highest during the ovulation phase, while progesterone levels are lowest during this phase, contradicting the notion that low estrogen levels produce TMD pain. In congruence with Villanova, Landi set out to investigate the role of hormones in young female TMD patients, finding that it was, in fact, the high levels of estrogen that affected the physiopathology of TMD, rather than low levels of estrogen [16].

Discussion

Previous studies have aimed to confirm the relationship between TMD and hormonal levels in young females. Results demonstrate a correlation between TMD pain and estrogen levels, but conflicting evidence exists regarding the exact type of correlation. Landi., *et al*. show higher estradiol levels leading to TMD pain [16]. On the contrary, LeResche., *et al*. demonstrated that lower estradiol leads to TMD pain, and Gunson., *et al*. determined that the condyle is negatively affected by these low levels [17,18]. However, it also concluded that fluctuations in estradiol levels can increase TMD pain [17]. Vilanova., *et al*. also showed that TMD pain levels vary throughout the menstrual cycle, correlating with the hormonal fluctuations seen throughout the menstrual cycle [19]. The data suggest that it may not be the actual higher or lower levels of estradiol leading to TMD pain. Instead, our theory is that the continually fluctuating estradiol levels lead to increased TMD pain in young females.

The fluctuation of hormones, their interactions, and how they affect the neuromuscular system may correlate with increased TMD pain. For instance, Vilanova., *et al*. suggest that pain modulation varies throughout the menstrual cycle. Rezaii., *et al*. found more effective pain management during ovulation than during the early follicular and mid-luteal phases [14,19]. Based on the hypothesis from Bi., *et al*. one plausible explanation may be that estrogen enhances hyperalgesia of inflamed TMJ via modulating voltage-gated Na^+ channels in the trigeminal ganglion [1]. Estrogen can have varying effects on pain mechanisms. Its effects on Na^+ channels may be one route of its variations during the menstrual cycle affecting pain. This might suggest that there is decreased pain with higher levels of estrogen during the ovulatory phase. However, the pain increases when the precipitous drop of estrogen occurs at the end of ovulation. This indicates that the interactions and fluctuations of estrogen could be affect how pain is perceived.

TMD pain that potentially occurs with these estrogen fluctuations may be associated with the inflammatory effects and damage that can occur with higher and lower estrogen levels. According to Wu., *et al*. 17-beta estradiol enhanced pain of inflammatory TMJ via hippocampus receptors in ovariectomized rats [2]. In line with that, Flake., *et al*. found that estrogen and inflammation positively affect TMJ afferent neurons in rats [3]. How estrogen enhances stimulation of proteins and neurons in rats may similar in that estrogen in females could inherently lead to irreversible inflammatory effects, thus correlating with increased TMD pain during hormonal fluctuations.

In addition, Gunson., *et al*. showed that with inflammatory markers, lower levels of estradiol do not allow the condyle to repair itself naturally [18]. Based on results from Cheng., *et al*. depending on the concentration of estrogen, it can affect the cell growth of condylar chondrocytes, which means that estrogen may be affecting the growth of mandibular condylar chondrocytes [4]. If this mechanism is seen in females, the varying concentrations of estradiol could directly influence TMD pain via its interactions with TMJ chondrocytes. This provides insight into one potential area where treatment can be targeted to relieve pain, the TMJ chondrocytes.

Just as mandibular chondrocytes may be affected, these estrogen fluctuations may cause direct destruction to other TMJ cellular components. Galal., *et al*. explored and confirmed the presence of estrogen alpha and beta receptors in joint cells [5]. Thus, estrogen directly affect the TMJ, leading to cellular damage and pain when hormonal fluctuations occur. However, it could also have the opposite effect. This can be seen during pregnancy when there are substantial fluctuations in hormones. In a prospective study from LeResche., *et al*. it was

evaluated that during pregnancy, musculoskeletal orofacial pain did in fact improve [6]. One theory regarding pain improvement is that the estrogen fluctuations that occur directly correlate to the TMJ.

An unexpected finding was seen regarding hormones and mastication. Goncalves., *et al*. demonstrated that hormonal fluctuation did not affect masticatory function, and Vilanova., *et al*. exhibited that TMD pain did not interfere with masticatory function in females [12,19]. In line with this, Yamada., *et al*. explored that in rat TMJ, estrogen receptor alpha is expressed [7]. This association allows the thought that hormonal influence on TMD pain is because there are estrogen receptors within the TMJ, but not within the muscles of mastication. This adds to the idea that there are many classifications of TMD, and it is imperative to distinguish the difference between muscle disorders versus joint disorders to develop appropriate treatments.

These results build on the evidence from LeResche., *et al*. that increased TMD pain may be associated with rapid estrogen change and Ribeiro., *et al*. that the variation in estrogen concentration ultimately determines what happens with inflammation and pain [15,17]. This supports our hypothesis that the fluctuations of hormones have the most prominent effect on the severity of TMD pain in females. In addition to affecting the TMJ, Kurokawa., *et al*. demonstrated that sex hormones can control cardiac ion channels [8]. These studies provide new insight into the relationship between sex hormones and their effects not only on pain and medical conditions. These hormones affect various medical conditions and could be potential targets when developing new treatments.

It is also important to remember that even though estradiol can significantly affect TMD pain in females, TMD is multifactorial. In addition to targeting treatment focused on estradiol receptors, focusing on other causes of TMD is imperative. According to Chisnoiu., *et al*. some causes include occlusal factors, parafunction, and psychological factors [9]. Furthermore, it has been shown that genetics may play a significant role in the risk of developing TMD. For instance, a study from Ribeiro-Dasilva., *et al*. explained how polymorphism in an estrogen receptor may predispose women to developing TMD [10]. The results that hormonal fluctuations may lead to increased TMD pain build on this existing evidence of how genetics can play a significant role in discrepancies of TMD pain. Additionally, other TMD risk factors should be considered when planning experimental research. Controls need to be in place so that the focus is on estradiol, without potential influence from other factors.

By learning about these discrepancies, it can provide better targets for treatment. Just as important as studying estrogen, it is just as imperative to studying testosterone and its effects on the TMJ. The data contributes a clearer understanding of estrogen fluctuations that negatively effect on female TMD Pain. However, testosterone may have positive effects on the TMJ. Fanton., *et al*. showed that in rats, the effects of testosterone on androgen receptors have protective mechanisms for TMD [11]. Although estrogen may have destructive capabilities for the TMJ, other discrepancies involved, as testosterone may have protective capabilities. This follows the idea that it all comes back to genetics and the interactions of various hormones.

One limitation of this systematic review is that the generalizability of the results may be limited. Also, the methodology included English-only research, limiting the scope of our results in the database search. In addition, some studies relied on self-reported data in a diary, while others relied on the participants' thorough history. Furthermore, it is beyond the scope of this study to determine exactly why this fluctuation of hormones leads to increased TMD pain, as further research is indicated.

Conclusion

This systematic review provides an overview of current research on the relationship between estrogen and TMD. The review aimed to determine what research states about the fluctuation of estrogen levels impacting TMD symptoms. A variety of studies dedicated to the effect of hormones, including estrogen, on TMD symptoms. However, our review has determined that the exact relationship of estrogen levels and TMD pain has conflicting results. Data can support this systematic review's central hypothesis that fluctuations of estrogen significantly impact TMD. However, it needs to be clarified exactly why these fluctuations may be occurring. The literature favors that it is the fluctuation of the levels that impact the symptom of pain rather than the high or low levels themselves. However the exact mechanism of the fluctuation and their influence on pain is unclear.

As a result, future clinical trials are needed to consider different reasons for the fluctuation of estrogen leading to increased TMD pain, such as hormonal imbalances, fibromyalgia, or other autoimmune disorders. Further research should focus on the mechanisms behind estrogen levels leading to increased TMD inflammation. Additionally, controls need to be placed to ensure that the effects of estradiol levels are the focus and can rule out other factors. This will aid in developing treatment options that target TMD pain. Other avenues include analyzing if these fluctuations affect the TMD more than other joints. Furthermore, testosterone trials are needed to understand better potential protective mechanisms contributing to the discrepancies in TMD pain.

Due to the inconsistencies between the results of the studies, this systematic review cannot conclusively determine the exact relationship between the fluctuation of estrogen and TMD symptoms. Additionally, the review unveiled further questions about the effects of testosterone and its influence on variability of TMD symptoms seen between males and females. Considering TMD affects such a large population, future research is advised to establish a better understanding between fluctuating estradiol and TMD pain, to tailor treatment, and to provide advances in therapy care for TMD patients.

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