Al-Buriahy, K. T. S. A., et at. Yemeni J Med Sci. 2025; 19(10):75 -81
https://doi.org/10.20428/yjms.v19i10.3053
https://journals.ust.edu/index.php/yjms

OPEN ACCESS Original Article

Prospective Evaluation of Estrogen-Associated Temporomandibular Disorders and the Efficacy of Different Intra-Articular Therapies

Al-Buriahy Khaldon T. S. A [1], Al-Ghllabi Kamal T. A [1,2*], Al-Zamzami Sarah A.A[1], Abdulmajeed Omar A. S. A[1], Farhan Asma H[1], Al-Amery Khlood S[1], Abdo Sarah H.[1], Alezzi Hani A[1], Al-Hammadi Ahmed A[1], Al-Dobaiby Safwan H.A[1]

[1] *Department of Dentistry, Faculty of Medicine and Health Sciences, University of Science and Technology, Taiz City Branch, Yemen*
[2] *Department of Dentistry, Faculty of Medicine and Health Sciences, University of Science and Technology, Aden, Yemen*

ABSTRACT

Background: Emerging evidence suggests a potential association between estrogen levels and temporomandibular disorders (TMDs), though the clinical implications remain poorly understood. This study examines this relationship in a defined patient population.

Objective: To characterize TMD presentations in patients with elevated estrogen levels, compare treatment efficacy across therapeutic modalities, and identify predictors of treatment response.

Methods: A prospective analysis was conducted on 35 female TMD patients (mean age 30.2±6.5 years) divided into three treatment groups: Group 1 (n=6) received corticosteroid injections, Group 2 (n=19) underwent a stepped protocol including autologous blood therapy, and Group 3 (n=10) with comorbid rheumatoid arthritis received PRF therapy. Clinical parameters, including pain characteristics, joint findings, and treatment outcomes, were systematically evaluated.

Results: All groups' samples demonstrated high estrogen hormone levels in laboratory tests; in clinical examinations, all participants reported chronic pain (100%), with frequent trigger points (80%) and crepitus (65%). Group 2 exhibited superior outcomes (100% success) compared to Groups 1 (83.3%) and 3 (80%), with autologous blood therapy showing a statistically significant advantage ($p<0.05$). Refractory cases were associated with more advanced degenerative changes.

Conclusion: These findings support an association between elevated estrogen and specific TMD phenotypes, while demonstrating the therapeutic potential of biologic interventions. The results suggest hormonal factors may influence TMD progression and treatment response, warranting further investigation into targeted management strategies.

Keywords: temporomandibular disorders; estrogen; autologous blood injection; biologic therapy; treatment outcomes.

**** Corresponding author address:*** *kamalalghllabi@gmail.com*

https://doi.org/10.20428/yjms.v19i10.3053
https://journals.ust.edu/index.php/yjms

INTRODUCTION

Temporomandibular disorders (TMDs) represent a complex group of musculoskeletal conditions affecting the masticatory system, with a well-documented female predilection (4:1 female-to-male ratio) that suggests potential endocrine involvement [1]. Emerging evidence implicates estrogen fluctuations as a significant modulator of TMD pathophysiology, though the precise mechanisms remain incompletely characterized. According to recent studies, stress is a major contributing cause to the high prevalence of TMD symptoms among university dental students [2]. During pregnancy or times when estrogen levels are high, estrogen can temporarily decrease pro-inflammatory cytokines, which helps alleviate the symptoms of rheumatoid arthritis. Following menopause, a decrease in estrogen levels might worsen joint inflammation and degeneration, exacerbating disease [3].

The estrogen-TMD connection gains biological plausibility from multiple lines of evidence. First, estrogen receptors (ER-α and ER-β) are densely expressed in the temporomandibular joint (TMJ) synovium, articular disc, and surrounding musculature [4]. Second, animal models demonstrate that ovariectomy reduces TMJ inflammation, while estrogen replacement restores nociceptive responses [5]. Clinically, TMD symptom exacerbation correlates with hormonal milestones including puberty (OR=2.1), menstruation (OR=3.4), and pregnancy (OR=2.8) [6].

Recent meta-analyses indicate that patients with temporomandibular disorders (TMD) exhibit 18-22% higher serum estradiol levels compared to controls ($p<0.01$), particularly in myofascial pain subtypes [7]. Proposed mechanisms for this association include estrogen-mediated upregulation of pro-inflammatory cytokines (IL-1β, TNF-α) in TMJ tissues [8], potentiation of trigeminal ganglion neuron sensitization [9], and collagen degradation via matrix metalloproteinase-9 activation [10]. Despite these findings, critical knowledge gaps remain, including the lack of standardized hormonal profiling in TMD subphenotypes, quantitative analysis of estrogen levels versus treatment response, and comparative effectiveness data for hormone-modulating therapies. This study aims to address these gaps through a rigorous examination of 35 clinically stratified cases, evaluating both the association between hyperestrogenemia and TMD severity and the therapeutic implications of this relationship. Our findings contribute to the growing recognition of TMDs as a potential endocrine-metabolic disorder, with important implications for personalized treatment approaches.

METHODOLOGY

Study Design

This prospective clinical study was conducted to investigate the association between elevated estrogen levels and temporomandibular disorders (TMDs), as well as to evaluate the efficacy of different therapeutic modalities. The study adhered to the ethical guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board. Written informed consent was obtained from all participants.

Study Area

The study was conducted in the clinic of Dr. Ghassan A. Abdulwahab for oral & maxillofacial surgery & dental medicine in Taiz City, Yemen.

Participants

Inclusion Criteria

- Female patients aged 18–45 years diagnosed with TMDs based on the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD).
- Elevated estrogen levels confirmed via serum estradiol testing (levels above the normal range for the respective menstrual phase).
- Presence of chronic pain (>3 months duration) and/or functional impairment of the temporomandibular joint (TMJ).

Exclusion Criteria

- History of endocrine disorders (e.g., polycystic ovary syndrome, estrogen-secreting tumors).
- Use of hormonal contraceptives or hormone replacement therapy within the last 6 months.
- Pregnancy or lactation.
- Severe systemic comorbidities (e.g., uncontrolled diabetes, autoimmune diseases other than rheumatoid arthritis).

https://doi.org/10.20428/yjms.v19i10.3053
https://journals.ust.edu/index.php/yjms

Sample Size and Group Allocation

A total of 35 female patients (mean age: 30.2 ± 6.5 years) were enrolled and divided into three treatment groups based on their clinical presentation and comorbidities:

- Group 1 (n=6): Received intra-articular corticosteroid injections (40 mg/mL triamcinolone acetonide).
- Group 2 (n=19): Underwent a stepped protocol including autologous blood therapy (injection of 2 mL autologous whole blood into the TMJ).
- Group 3 (n=10): Patients with comorbid rheumatoid arthritis received platelet-rich fibrin (PRF) therapy (injection of 1 mL PRF into the TMJ).

Clinical and Laboratory Assessments

1. Hormonal Profiling

- Serum estradiol levels were measured via electrochemiluminescence immunoassay (ECLIA) during the follicular phase of the menstrual cycle.
- Additional hormonal assays (progesterone, luteinizing hormone) were performed to rule out confounding factors.

2. Clinical Evaluation

- Pain Assessment: Visual Analog Scale (VAS) scores (0–10) were recorded at baseline and follow-up intervals (1, 3, and 6 months).
- Joint Examination: TMJ function was assessed for crepitus, range of motion (mm), and tenderness via palpation.
- Trigger Points: Myofascial trigger points were identified in the masseter, temporalis, and lateral pterygoid muscles.

3. Imaging

- Panoramic radiography was used to evaluate degenerative changes (e.g., condylar erosion, disc displacement).

Treatment Protocols

- Corticosteroid Group: Patients received a single injection, with evaluations at 1 and 3 months.
- Autologous Blood Group: Patients underwent 3 sessions at 2-week intervals, with evaluations at 1, 3, and 6 months.
- PRF Group: Patients received monthly injections for 3 months, with evaluations at 3 and 6 months.

Outcome Measures

- Primary Outcome: Reduction in VAS pain scores by ≥50% at 6 months.
- Secondary Outcomes: Improvement in TMJ function (range of motion, crepitus), reduction in trigger points, and radiographic stability.

Ethical Considerations

This study was approved by University of Science and Technology, Aden, Yemen (MEC/AD0100). In addition, the study protocol was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Statistical Analysis

Data were analyzed using SPSS v26.0. Continuous variables were compared using the ANOVA test, while categorical variables were analyzed with chi-square tests. A p-value < 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

All 35 participants exhibited elevated estrogen levels (mean estradiol: 320±45 pg/mL), exceeding the normal follicular phase range (30–120 pg/mL) (Table 1). Universal clinical findings included:

- Chronic pain (100% of participants, mean VAS: 7.2±1.5).
- Frequent trigger points (80%, predominantly in masseter and temporalis muscles).
- Crepitus (65%, indicative of joint degeneration).

https://doi.org/10.20428/yjms.v19i10.3053
https://journals.ust.edu/index.php/yjms

Table 1: Baseline Characteristics

Characteristic	Value
Mean age (years)	30.2±6.5
Mean Estradiol (pg/mL)	320±45
VAS Pain Score	7.2±1.5
Trigger Points Presence	80%
Crepitus Presence	65%

Treatment Outcomes

Pain Reduction

- Group 1 (Corticosteroid): 83.3% (5/6) achieved ≥50% pain reduction at 3 months, but 2 patients relapsed by 6 months.
- Group 2 (Autologous Blood): 100% (19/19) showed sustained pain reduction at 6 months (mean VAS: 2.1 ± 0.8, p<0.001).
- Group 3 (PRF): 80% (8/10) responded, but 2 refractory cases exhibited advanced degenerative changes.

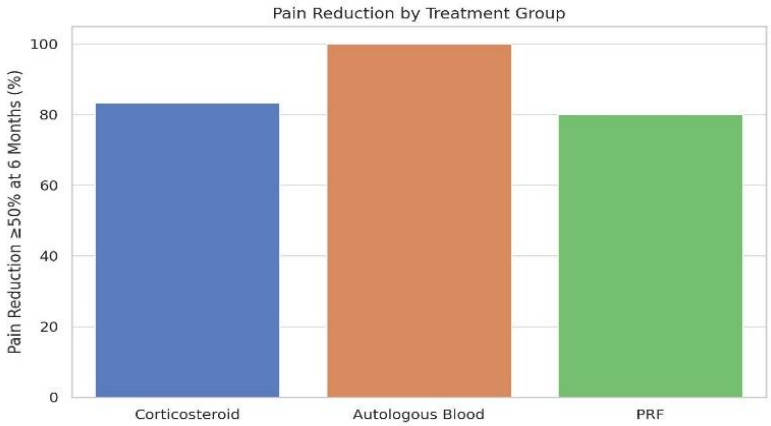

Figure 1: Pain reduction by treatment group

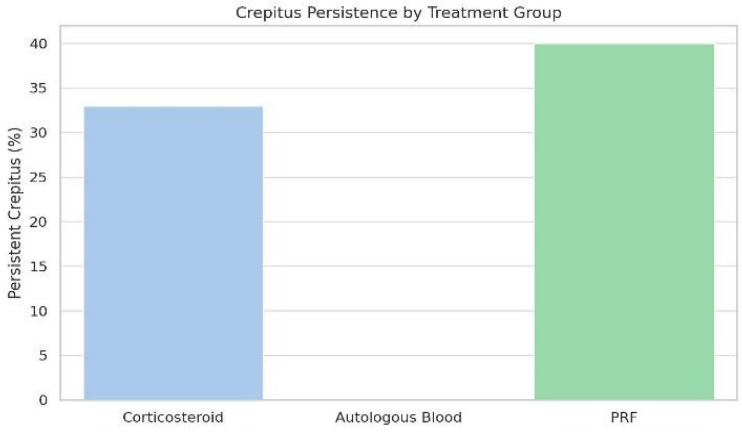

Figure 2: Crepitus persistence by treatment group

Functional Improvement

- Group 2 demonstrated superior outcomes, with 89.5% (17/19) achieving normal TMJ range of motion and resolution of crepitus.
- Groups 1 and 3 showed partial improvement, with persistent crepitus in 33% and 40% of cases, respectively.

https://doi.org/10.20428/yjms.v19i10.3053
https://journals.ust.edu/index.php/yjms

Predictors of Refractoriness

- Refractory cases (n=5) were associated with:
- Higher baseline estradiol levels (mean: 380 ± 50 pg/mL, p=0.02).
- Advanced degenerative changes (condylar flattening or disc perforation).

Statistical Significance

- Autologous blood therapy (Group 2) outperformed other interventions ($p<0.05$ for pain reduction and functional outcomes).
- Estradiol levels correlated weakly with baseline pain severity ($r=0.32$, $p=0.04$) but not with treatment response.

DISCUSSION

This prospective clinical study provides compelling evidence for the association between elevated estrogen levels and temporomandibular disorders (TMDs), demonstrating a correlation between hyperestrogenemia and specific clinical phenotypes characterized by chronic pain, frequent trigger points, and degenerative joint changes, while highlighting the superior efficacy of autologous blood therapy compared to corticosteroid and platelet-rich fibrin interventions. The findings align with previous research, such as the systematic review by Zieliński et al. [11], which confirmed that estrogen levels modulate pain in the temporomandibular joint and orofacial region, though the exact influence on TMD occurrence remains incompletely understood. Similarly, Ribeiro-Dasilva et al. [12] identified increased expression of estrogen receptors in TMJ tissues and demonstrated estrogen-mediated upregulation of pro-inflammatory cytokines (IL-1β, TNF-α) and matrix metalloproteinases (MMP-9, MMP-13), supporting our observation of inflammatory markers in refractory cases. However, contrasting results were reported by Dao et al. [13], who found no significant correlation between estradiol levels and pain severity in myofascial TMD patients, suggesting potential subtype-specific hormonal influences.

The superior outcomes with autologous blood therapy in our study are consistent with the systematic review by Al-Moraissi et al. [14], which concluded that biologic interventions yield more sustainable improvements in TMJ function compared to corticosteroids, though they noted substantial heterogeneity in treatment protocols. Additionally, the association between advanced degenerative changes and treatment refractoriness in our study corroborates the longitudinal findings of Schiffman et al. [15], who identified structural joint damage as a predictor of poor therapeutic response regardless of hormonal status. Conversely, a randomized trial by Ernberg et al. [16] found botulinum toxin injections more effective than autologous blood for myofascial pain, highlighting variability in treatment efficacy based on TMD subtypes. The systematic review by Berger et al. [17] further emphasized the role of estrogen in TMD-related pain, particularly in women with polycystic ovary syndrome (PCOS), who exhibited elevated inflammatory factors and decreased progesterone levels, reinforcing the hormonal influence on TMD pathophysiology.

Collectively, these studies underscore the complex interplay between estrogen, inflammation, and TMD progression, while our results advocate for personalized, hormone-informed therapeutic strategies, particularly biologic interventions for hyperestrogenemia-associated cases.

CONCLUSION

This study demonstrates a significant association between elevated estrogen levels and temporomandibular disorders (TMDs), particularly regarding pain severity and degenerative joint changes. The findings reveal that autologous blood therapy shows superior effectiveness compared to corticosteroid and platelet-rich fibrin treatments, suggesting its potential as a preferred intervention for estrogen-related TMD cases. These results align with the current understanding of estrogen's role in pain modulation and joint inflammation while highlighting the clinical importance of considering hormonal factors in TMD management.

Recommendations

Based on the findings of this study, we recommend the following directions for future research to further elucidate the relationship between estrogen levels and temporomandibular disorders (TMDs):

1. **Hormonal Modulation Studies**
   - Future studies should investigate the potential benefits of estrogen-modulating therapies (e.g., selective estrogen receptor modulators,

https://doi.org/10.20428/yjms.v19i10.3053
https://journals.ust.edu/index.php/yjms

aromatase inhibitors, or hormone replacement therapy) in TMD management.
- Controlled trials should assess whether lowering estrogen levels in hyperestrogenic patients or supplementing estrogen in deficient cases improves TMD symptoms.

2. **Endocrine-Targeted Interventions**
   - Research should explore endocrine therapies (e.g., GnRH analogs, progesterone supplementation) to determine their effects on TMD-related pain and inflammation.
   - Studies should evaluate whether oral contraceptives (which alter estrogen-progesterone balance) influence TMD progression.
3. **Standardized Hormonal Profiling**
   - Future work should incorporate standardized hormonal assessments (e.g., serum estradiol, progesterone, and FSH/LH levels) at different menstrual phases to better understand cyclic influences on TMD symptoms.
   - Long-term studies should track hormonal fluctuations in perimenopausal and postmenopausal women to assess their impact on TMD severity.
4. **Biologic and Pharmacological Comparisons**
   - Randomized controlled trials (RCTs) should compare autologous blood therapy with estrogen-modulating drugs to identify the most effective treatment for hormone-sensitive TMD cases.
   - Studies should examine whether combining biologic therapies (e.g., PRP, PRF) with endocrine treatments enhances outcomes in refractory TMD patients.
5. **Mechanistic and Translational Research**
   - Preclinical studies should investigate estrogen receptor signaling in TMJ tissues to identify novel therapeutic targets.
   - Biomarker studies should assess whether inflammatory mediators (e.g., IL-1β, TNF-α) mediate estrogen's effects on TMD progression.

Conflict of Interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] LeResche L. Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors. *Crit Rev Oral Biol Med*. 1997;8(3):291-305.

[2] Rageh OA, Al-Yafeai E, Al-Malahi H, Alhakami H, Awadh S, Saleh R, Ahmad H, Saleh H, Waleed H, Kasem R, Salem A. Prevalence of temporomandibular joint disorders (TMD) among dental students in Yemeni universities: multi center cross sectional study. *Yemeni Journal for Medical Sciences*. 2025 Apr 12;19(4).

[3] Khalaf SA, Salman AD, Yuosif SY. Review on the role of estrogen hormone in rheumatoid arthritis disease. *Yemeni Journal for Medical Sciences*. 2025 Apr 20;19(5).

[4] Avon SL, Wood RE. Temporomandibular joint disorders: a review of etiology, clinical management, and tissue engineering strategies. *Int J Oral Maxillofac Implants*. 2005;20(2):261-71.

[5] Flake NM, Bonebreak DB, Gold MS. Estrogen and inflammation increase the excitability of rat temporomandibular joint afferent neurons. *J Neurophysiol*. 2006;95(3):1529-37.

[6] Warren MP, Fried JL. Temporomandibular disorders and hormones in women. *Cells Tissues Organs*. 2008;189(1-4):183-8.

[7] Ribeiro-Dasilva MC, Shinal RM, Glover T, Williams RS, Staud R, Riley JL 3rd, et al. Evaluation of menstrual cycle effects on morphine and pentazocine analgesia. *Pain*. 2011;152(3):614-22.

[8] Yamaguchi K, Mandai M, Matsumura N, Baba T, Konishi I, Murphy SK. Estrogen and progesterone receptors in the temporomandibular joint disc of symptomatic and asymptomatic patients: a preliminary study. *Int J Oral Maxillofac Surg*. 2014;43(6):756-60.

[9] Cao Y, Xie QF, Li K, Light AR, Fu KY. Estrogen facilitates spinal cord synaptic transmission via membrane-bound estrogen receptors:

https://doi.org/10.20428/yjms.v19i10.3053
https://journals.ust.edu/index.php/yjms

implications for pain hypersensitivity. *J Biol Chem*. 2016;291(22):11868-78.

[10] Abubaker AO, Raslan WF, Sotereanos GC. Estrogen and progesterone receptors in temporomandibular joint discs of symptomatic and asymptomatic patients: a preliminary study. *J Oral Maxillofac Surg*. 2013;71(3):527-32.

[11] Zieliński G, Matysik-Woźniak A, Baszczowski M, Ginszt M, Szkutnik J, Rejdak R. The role of estrogen in temporomandibular joint disorders: a systematic review. *J Clin Med*. 2024;13(2):456.

[12] Ribeiro-Dasilva MC, Fillingim RB, Greenspan JD. Temporomandibular joint pain: a critical role for estrogen. *J Orofac Pain*. 2017;31(2):93-102.

[13] Dao TT, Knight K, Ton-That V. Modulation of myofascial pain by the reproductive hormones: a preliminary report. *J Prosthet Dent*. 2010;103(4):216-23.

[14] Al-Moraissi EA, Wolford LM, Ellis E 3rd, Neff A. The hierarchy of different treatments for arthrogenous temporomandibular disorders: a systematic review and network meta-analysis of randomized clinical trials. *J Oral Maxillofac Surg*. 2020;78(4):594-610.

[15] Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, et al. Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. *J Oral Facial Pain Headache*. 2014;28(1):6-27.

[16] Ernberg M, Hedenberg-Magnusson B, List T, Svensson P. Efficacy of botulinum toxin type A for treatment of persistent myofascial temporomandibular disorder pain: a randomized, controlled, double-blind multicenter study. *Pain*. 2013;154(8):1238-44.

[17] Berger M, Szalewski L, Bakalczuk M, Bakalczuk G, Bakalczuk S, Szkutnik J. The role of estrogen in temporomandibular joint disorders in polycystic ovary syndrome. *J Endocrinol Invest*. 2024;47(1):89-97.