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ORIGINAL ARTICLE

The Effects of Changes in Serum Estrogen Combined with Occlusal Interference on the Morphology of Condylar Tissue and Estrogen Receptor Expression in Rats

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Abstract

Objective: This study aimed to explore the contributions of estrogen fluctuations and mechanical occlusal factors to the pathogenesis of idiopathic condylar resorption (ICR) in a rat model.

Methods: An ovarian insufficiency model was established in female Sprague-Dawley (SD) rats using cisplatin, followed by the administration of a short-term oral contraceptive to manipulate estrogen levels. Occlusal interference was introduced via dental pins. Serum estradiol (E2) concentrations were measured at baseline, day 15, and week 12. Histopathological changes were assessed through H&E staining, and the expression of estrogen receptors ERα and ERβ was evaluated immunohistochemically.

Results: The serum E2 levels significantly decreased in the experimental groups compared to controls ($P < 0.05$), correlating with notable histopathological changes in condylar cartilage, including reduced thickness and disordered cellular arrangement. Furthermore, expression levels of ERα and ERβ were significantly reduced in the experimental groups, indicating altered responsiveness to estrogen signaling with the combined effects of hormonal manipulation and mechanical interference.

Conclusion: Estrogen and mechanical occlusal factors play critical roles in the pathogenesis of ICR. The findings underscore the need for integrated approaches to managing TMJ disorders that consider both hormonal and mechanical influences. Future research should address the long-term implications of these interactions on condylar health.

Keywords: idiopathic condylar resorption, temporomandibular joint, estrogen, occlusal interference, estrogen receptor

Introduction

Idiopathic condylar resorption (ICR), also known as progressive condylar resorption, is described as an uncommon and aggressive degenerative condition of the temporomandibular joint (TMJ). This pathology primarily affects adolescent girls and young women, particularly during their pubertal growth spurts. ICR is characterized by the loss of condylar bone mass and leads to changes in skeletal structure, including a decrease in mandibular ramal height, steep mandibular and occlusal plane angles, as well as the development of anterior open bite [1-2]. Exact causes of ICR remain poorly understood, which is reflected in its designation as idiopathic, signifying that no identifiable cause has been determined. Various theories about its pathogenesis have been proposed, including hormonal imbalances, avascular necrosis, and dysfunctional remodeling of bone [3]. This lack of clarity complicates both diagnosis and management of the condition.

Research indicates that estrogen interacts with its receptors—estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ)—to influence the biological processes involved in the remodeling and homeostasis of the TMJ. Estrogen, particularly 17β-estradiol (E2), is recognized for

its role in modulating matrix turnover in various connective tissues, including TMJ fibrocartilage. It is hypothesized that the effects of E2 on condylar resorption are mediated through the activation of ERα and ERβ, which can trigger different pathways and outcomes in the context of tissue remodeling. Studies demonstrate that estrogen signaling via ERα significantly contributes to the regulation of matrix metalloproteinases (MMPs), specifically MMP-9 and MMP-13, which are pivotal in extracellular matrix (ECM) degradation. For instance, the upregulation of MMP-9 in response to E2 has been shown to lead to loss of collagen and glycosaminoglycans in TMJ fibrocartilage, contributing to the pathophysiology of TMJ disorders, including ICR [4-5]. Conversely, the contribution of ERβ to this process remains less well-defined, with some studies suggesting it may exert antagonistic effects to ERα in various contexts within tissue biology, including the TMJ. The dual expression of both receptors in TMJ fibrocartilage adds a layer of complexity to understanding how these pathways interact during the resorption process. However, the prevalence of ICR is notably higher in females, particularly during reproductive years, implying a strong link with fluctuations in estrogen levels throughout the menstrual cycle and menopause.

One significant contributor to condylar resorption is the local occlusal pressure. When this pressure exceeds the compensatory capacity of the joint, the natural bone remodeling processes can become impaired. This disruption can lead to pathological changes in the condyle, including increased bone absorption [6]. Researches have indicated that various mechanical stresses, such as excessive occlusal forces, can impact the condylar morphology. In circumstances where the applied load is beyond what the joint can accommodate, remodeling efforts may fail to keep pace with the mechanical demands placed on the TMJ [7]. This catabolic response leads to a reduction in condylar volume, exposing the bone to risks associated with degenerative changes and a decline in structural integrity [8]. However, the relationship between occlusal force and condylar morphology has been emphasized in research that correlates lower occlusal forces with smaller mandibular condyles. This suggests that occlusal instability not only affects functional dynamics but also instigates bone resorption processes that further compromise condylar health. Therefore, understanding the balance between mechanical loading and the biological response of the condyle is critical for both diagnosing and treating TMJ-related disorders.

In this study, an ovarian insufficiency model was established in Sprague-Dawley (SD) rats using cisplatin, followed by a short-term oral contraceptive regimen to manipulate estrogen levels and induce occlusal interference with a dental pin. The effects on condylar morphology were evaluated through H&E staining, and immunohistochemical assessment of estrogen receptors ERα and ERβ. This investigation aims to enhance our understanding of the relationship between estrogen and occlusal dynamics, shedding light on the mechanisms involved in dental and maxillofacial pathology.

Materials and Methods

Experimental Animals

Several healthy, unmated female SD rats, aged 6 weeks and weighing approximately (180 ± 10) g, were utilized for the study. The rats were housed under standard laboratory conditions, with natural lighting, an environmental temperature maintained between 22-25°C, and bedding changed every other day. All rats had ad libitum access to food and water throughout the experiment.

Grouping Design

Prior to the experiment, vaginal smears were performed to select 50 rats exhibiting normal estrous cycles. The rats were then randomly divided into five groups: A, B, C, D, and E, with 10 rats in each group. Rats in groups A and B were administered cisplatin via intraperitoneal injection for 14 days to establish an ovarian insufficiency model, thereby reducing serum estrogen levels. Rats in groups C and D were fed a short-term oral contraceptive (deoxymethy ltestosterone) for 12 weeks to interfere with serum estrogen levels. A dental pin, elevated by 1 mm, was embedded into the occlusal surface of the posterior teeth on one side of the rats in groups B and D to introduce occlusal interference. Rats in group E were given free access to food and water without any treatments.

Serum Estradiol Concentration Measurement

Blood samples were collected from the tails of the

rats prior to the experiment, on day 15, and at week 12. After centrifugation at 3000 rpm for 20 minutes, the serum was stored at -20°C until analysis. Estradiol concentrations were measured using the enzyme-linked immunosorbent assay method. Serum samples were diluted as necessary, and estradiol standards were prepared. A 96-well microplate was coated with estradiol monoclonal antibody and incubated overnight at 4°C. After blocking to prevent non-specific binding, diluted samples and standards were added and incubated for 2 hours. Following further washing, a secondary enzyme-conjugated antibody was added and incubated for 1 hour. After adding a substrate solution to develop color, a stop solution was applied to terminate the reaction, and absorbance was measured using a microplate reader. Estradiol concentrations were determined by comparing the absorbance values to a standard curve.

Condylar Morphological Observation

At week 20 of the experiment, the rats from each group were euthanized using excessive ether. The heads of the rats were immobilized using a custom cranial positioning frame, and the condylar tissue was carefully dissected, with attached muscles and ligaments removed. The tissue was then fixed in 10% formalin for 48 hours and decalcified in 5% nitric acid, with the nitric acid solution changed daily. After routine dehydration, the specimens were embedded in paraffin, ensuring that the mandible was oriented parallel to and in close contact with the paraffin embedding surface for consistent slicing. Continuous sagittal sections of the temporomandibular joint were cut at a thickness of 4 μm and stained with H&E for microscopic observation.

Immunohistochemical Staining

Additional tissue sections from paraffin-embedded samples were deparaffinized in xylene and rehydrated through graded ethanol. Antigen retrieval was performed in EDTA buffer (pH 9.0) by heating in a microwave for 10 minutes, followed by cooling. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 10 minutes. After washing in PBS, sections were incubated with a blocking serum for 30 minutes to reduce non-specific binding. Primary antibodies against estrogen receptors ERα (Santa Cruz, sc-8005) and ERβ (Santa Cruz, sc-390243) were applied and incubated overnight at 4°C. After washing, a biotinylated secondary antibody was added for 1 hour, followed by an avidin-biotin complex for 30 minutes. Visualization was achieved with a DAB substrate solution, resulting in brown color development at the antigen site. Sections were counterstained with hematoxylin and dehydrated. Under a light microscope, for each group of sections, the transitional and hypertrophic layers of the condylar cartilage were selected.

Statistical Analysis

Statistical analysis of the data was performed using SPSS version 20.0. Comparisons among multiple groups were conducted using one-way ANOVA, while comparisons between two groups were carried out using an independent samples t-test. An F-test was used to assess the homogeneity of variances among the groups. Protein expression were evaluated using a Chi-square test. A p-value of <0.05 was considered to indicate statistically significant differences.

Results

Serum E2 Concentration

The serum E2 concentrations were measured at three different time points: before the experiment, on the 15th day, and at the 12th week, across Group A, B, C, D and Group E (Figure 1)

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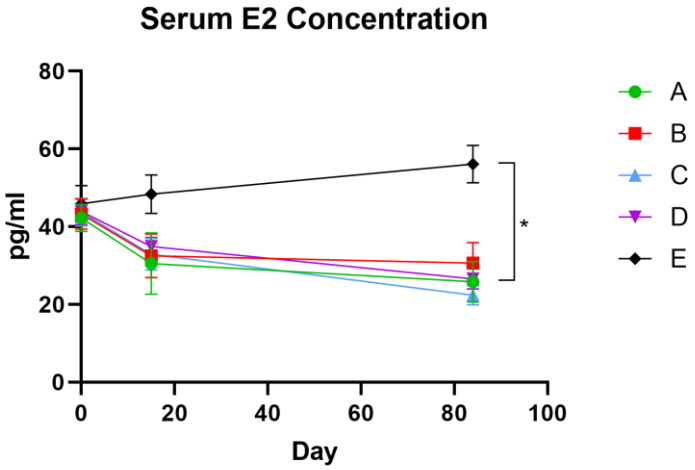

Figure 1. The serum E2 concentration before the experiment, on the 15th day, and at the 12th week, across Group A, B, C, D and Group E.

At the baseline (before the experiment), serum E2 concentrations for all groups were similar, with no statistically significant differences observed ($P > 0.05$). The concentrations were as follows: Group A: 43.23 ± 5.43 pg/ml, Group B: 43.98 ± 6.82 pg/ml, Group C: 44.23 ± 6.22 pg/ml, Group D: 44.05 ± 5.44 pg/ml, and Group E: 44.12 ± 6.12 pg/ml.

By the 15th day, a significant reduction in serum E2 concentrations was observed in the experimental groups compared to the control group (Group E: 47.12 ± 5.03 pg/ml).

Specifically, Group A showed a decrease to 30.63 ± 8.94 pg/ml, Group B to 31.72 ± 7.62 pg/ml, Group C to 32.89 ± 6.07 pg/ml, and Group D to 34.15 ± 4.46 pg/ml, with all comparisons yielding P-values < 0.05. This indicates significant differences between the control group and each of the experimental groups at this time point. At the 12th week, serum E2 concentrations continued to differ between the groups. Group E maintained the highest concentration at 56.29 ± 10.06 pg/ml, while Group A, Group B, Group C, and Group D recorded concentrations of 27.63 ± 6.72 pg/ml, 30.43 ± 8.35 pg/ml, 24.18 ± 5.03 pg/ml, and 26.96 ± 6.17 pg/ml, respectively. Statistically significant reductions were observed in all experimental groups compared to the control group ($P < 0.05$) (Table 1).

Table 1 Serum E2 Concentration

Group	n	Serum E2 Concentration (x±s,pg/ml)		
		Before	15th Day	12th Week
A	10	43.23±5.43	30.63±8.94	27.63±6.72
B	10	43.98±6.82	31.72±7.62	30.43±8.35
C	10	44.23±6.22	32.89±6.07	24.18±5.03
D	10	44.05±5.44	34.15±4.46	26.96±6.17
E	10	44.12±6.12	47.12±5.03	56.29±10.06

T Test were applied to compare the serum E2 concentration between groups.

Histopathological Changes in the Condyle

After H&E staining, the morphology of the condyle was clearly observable under a light microscope, with the cartilage layer divided into four distinct structures: the fibrous layer, proliferation layer, chondrocyte layer, and hypertrophic layer, each exhibiting different cellular morphologies. In the E group, the condylar cartilage layer was well-defined, with orderly cell arrangement, intact structure, and uniform consistency. The fibrous layer had a smooth surface, hypertrophic cells exhibited large nuclei oriented perpendicularly to the joint surface, and subchondral bone development was robust, with dense trabecular structure and distinct

reticular patterns (Figure 2).

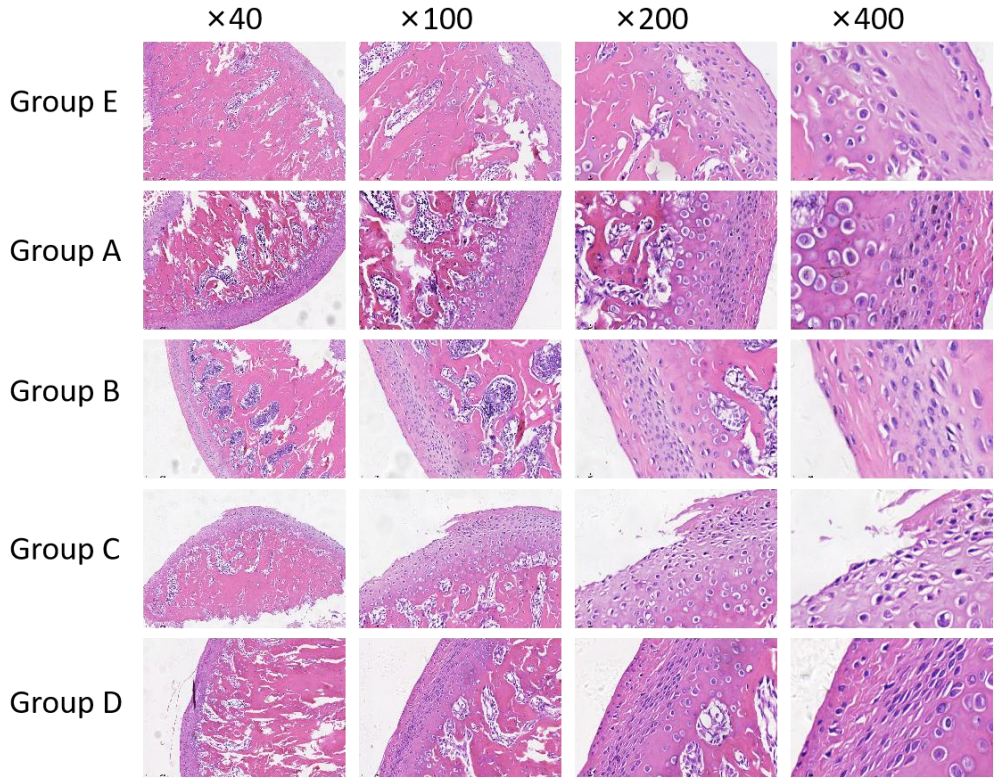

Figure 2. Histopathological changes in the condyle across Group A, B, C, D and Group E (H&E staining, ×40/×100/×200/×400)

In the A group, the cartilage layer was noticeably thinner, with smaller nuclear size, immature chondrocyte development, disordered cell arrangement, and severe cartilage layer fibrosis; subchondral trabecular bone was reduced (Figure 2). In the B group, the fibrous layer was significantly thinner, with a rough surface and marked collagenization, fibrous tissue proliferation, reduced hypertrophic cell volume and quantity, and sparse, disorganized subchondral trabecular bone (Figure 2). In group C (Figure 2), the fibrous layer of the condyle showed partial loosening, with a reduction in cartilage layer thickness. The arrangement of chondrocytes was disordered and immature. Additionally, there was a significant decrease in the number of trabecular structures, which appeared disorganized, with a loose architecture and absence of reticular structures. The medullary cavity was enlarged. The D group showed an irregular condylar surface, a thinning hypertrophic layer, and alternating areas of chondrocyte proliferation and degeneration (Figure 2), while subchondral bone showed no obvious changes.

Expression of ERα and ERβ in Condylar Cartilage

ERα and ERβ were expressed in the nuclears of condylar cartilage. The metrics were categorized into four grades based on the percentage of positive cells: 10%-25% (Grade I, 1 point), 26%-50% (Grade II, 2 points), 51%-75% (Grade III, 3 points), and 76%-100% (Grade IV, 4 points). Staining intensity was classified as light yellow (Grade I, 1 point), yellow (Grade II, 2 points), and brownish-yellow (Grade III, 3 points). The final expression strength was calculated as the product of the scores: 1-3 points (+), 4-6 points (++), and ≥8 points (+++).

Table 2 Expression of ERα and ERβ in Condylar Cartilage

Group	ERα (n %)		ERβ (n %)	
	-/+	++/+++	-/+	++/+++
A	3 (30%)	7 (70%)	5 (50%)	5 (50%)

B	5 (50%)	5 (50%)	4 (40%)	6 (60%)
C	4 (40%)	6 (60%)	6 (60%)	4 (40%)
D	5 (50%)	5 (50%)	4 (40%)	6 (60%)
E	0 (0%)	10 (100%)	2 (20%)	8 (80%)

Pearson χ^2, Continuity Correction and Fisher's Exact Test were applied to compare ERα and ERβ expression between groups

Table 2 presents the expression of estrogen receptors ERα and ERβ in condylar cartilage across groups. Compared to the E group, the expression strength of ERα and ERβ in the condylar cartilage of the A, B, C, D group was significantly reduced ($P < 0.05$) (Figure 3).

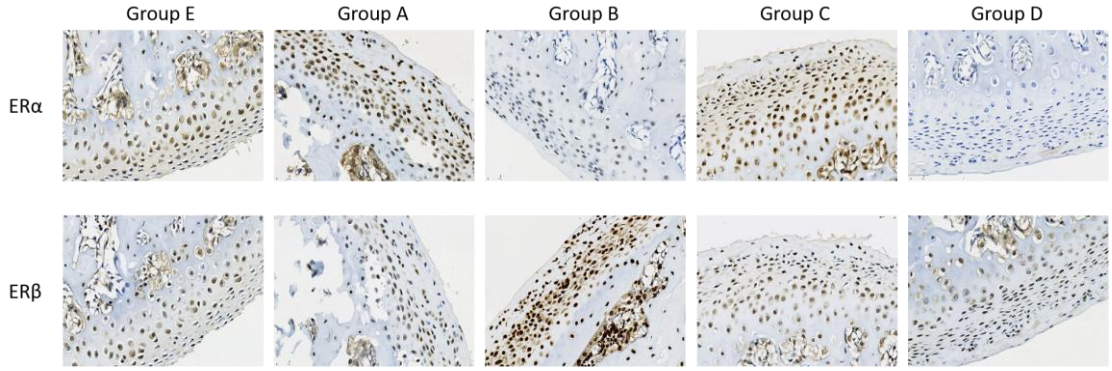

Figure 3. The expression of ERα and ERβ in condylar cartilage across Group A, B, C, D and Group E (Immunohistochemical staining, ×200).

However, in the B and D groups with combined occlusal interference, the decrease in ERα expression strength was greater than that of ERβ, while this phenomenon was not observed in the A and C groups with only hormonal interference (Figure 4).

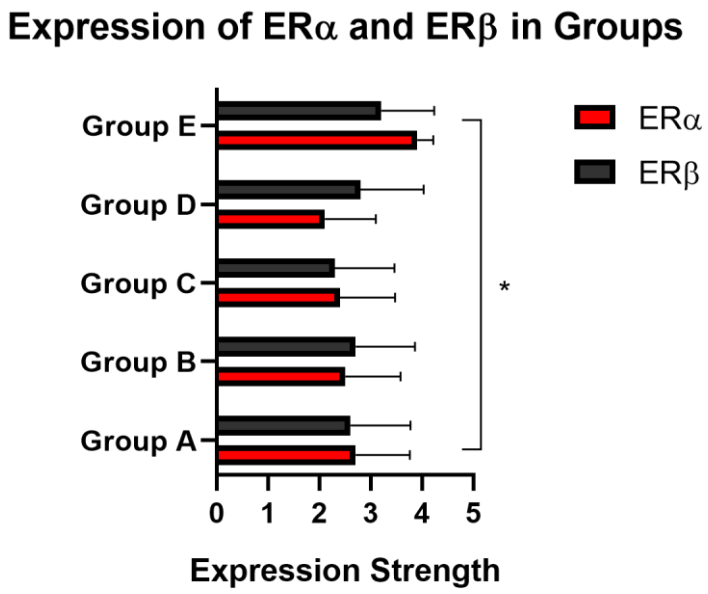

Figure 4 Comparison of the expression intensity of ERα and ERβ in Group A, B, C, D and the control Group E

Discussion

ICR is a complex and multifactorial condition primarily impacting young females, with estrogen fluctuations playing a critical role in its pathogenesis. In particular, the studies suggest that decreased estrogen levels can result in a more

pronounced breakdown of bone structure, leading to conditions like osteoporosis that may indirectly influence the onset of ICR [9]. Research indicates that female patients, particularly those in younger and reproductive age ranges, experience changes associated with their menstrual cycle. For instance, lower estrogen levels, such as those experienced during the follicular phase or post-ovariectomy, may lead to a pro-inflammatory response, which is hypothesized to increase the likelihood of condylar resorption and development of related symptoms [10]. In contrast, higher estrogen concentrations observed during ovulation and pregnancy appear to confer protective benefits against ICR, likely by promoting bone health and dampening inflammatory responses [11]. Furthermore, due to the complex interplay between mechanical loading and hormonal fluctuations, events such as orthodontic procedures may complicate the condition. In patients with ICR, the increase in mechanical stress from misalignment or incorrect loading might exacerbate osteoclastic activity, especially when compounded by low estrogen levels [12]. This suggests a dual role for estrogen—not only in maintaining bone density but also in modulating the inflammatory environments that can contribute to bone resorption.tigations into the molecular mechanisms at play have pointed to the role of estrogen receptors in local immune response modulation. Estrogen signaling pathways may influence the activity of osteoclasts—cells responsible for bone resorption—where estrogen not only promotes apoptosis in these cells but also regulates inflammatory responses in the subchondral bone and surrounding tissues [13]. The findings of this study emphasize the significant contribution of hormonal interference and mechanical occlusal factors in modulating condylar morphology and estrogen receptor expression, particularly ERα and ERβ. The observed reductions in serum estradiol (E2) levels in the experimental groups, especially with concurrent manipulation via cisplatin and oral contraceptives, underscore the importance of estrogen in maintaining condylar homeostasis and structural integrity. Changes in serum E2 concentrations align with the histopathological alterations observed, further highlighting the impact of diminished estrogen levels on condylar health.

The histopathological results illustrate significant degenerative changes in the condylar cartilage among the experimental groups compared to the control group. Specifically, reductions in cartilage thickness, disordered chondrocyte arrangement, and decreased trabecular bone density indicate an adverse response to both hormonal manipulation and mechanical interference. The findings suggest that the detrimental effects of estrogen depletion are exacerbated by occlusal pressures, further impairing the normal remodeling processes of the TMJ. This relationship aligns with existing literature highlighting the interdependence of hormonal and mechanical factors in the pathogenesis of bone-related conditions, reinforcing the necessity for a multifaceted approach in evaluating ICR. In various studies, the affected cartilage typically exhibited signs of degeneration characterized by disorganization and structural alterations. For instance, evaluations conducted included H&E staining, which displayed a fibrotic and sclerotic extracellular matrix along with a decreased presence of chondrocytes compared to healthy cartilage, showcasing the detrimental impact of ICR on cartilage quality [14]. Furthermore, significant reductions in glycosaminoglycan content were documented through safranin O staining, a marker indicative of cartilage integrity and health. This depletion reflects a loss of proteoglycan components crucial for maintaining the biochemical and biomechanical properties of cartilage. The changes in gene expression were also highlighted, indicating that chondrogenic markers such as type II collagen (Col II) and SOX9 were downregulated in the context of ICR, suggesting impaired chondrogenesis and cartilage repair capabilities. In the context of ICR, other markers such as ADAMTS-5, which is typically associated with cartilage degradation, were found to be upregulated, reinforcing the notion of ongoing catabolic processes within the affected tissue. Compounding these findings, necrotic chondrocytes were observed, with the nuclei appearing pyknotic, indicating cell death and further corroborating the degenerative changes occurring in the articulating surfaces [15]. The histopathological approach allows for a comprehensive understanding of the complex alterations present in the condylar cartilage due to ICR, highlighting a combination of cellular degeneration, matrix degradation, and altered

gene expression patterns that contribute to the pathology of this condition.

ERα is widely expressed in various tissues, including cartilage, synovial fibroblasts, and bone cells, indicating its involvement in the modulation of physiological processes in the joints. In the context of TMJ disorders, studies have shown that ERα is present in TMJ fibrocartilage, where its expression is influenced by estrogen levels. The role of ERα in this scenario is critical as its action leads to both matrix loss and potential changes in cartilage tissue architecture [5]. Similarly, in RA, ERα expression is linked to joint inflammation and bone remodeling processes. It has been observed that estrogen influences the behavior of various joint cell types, including osteoblasts and osteoclasts, via ERα. In particular, estrogen has an anabolic effect on bone by promoting osteoblast function, while its deficiency, as seen in postmenopausal women, is associated with increased bone resorption and joint damage [16]. While the specific mechanisms by which ERβ functions in joint tissues and its interaction with other signaling pathways require further elucidation, its expression in joints signifies a crucial pathway through which estrogen may exert protective effects and modulate inflammation and joint integrity. The expression analysis of ERα and ERβ revealed significant reductions in the experimental groups compared to controls, reflecting the altered responsiveness of the condylar cartilage to estrogen signaling. The differential impact of occlusal interference on ERα expression compared to ERβ may point to a complex interaction between these receptors in modulating tissue remodeling processes. Notably, the more pronounced reduction of ERα expression in groups with combined interference suggests that mechanical stressors may further influence hormonal pathways, emphasizing the need for further exploration into the interplay between mechanical and hormonal signals in TMJ health.

Despite the insights gained from this study, certain limitations must be acknowledged. The reliance on a rat model, while providing valuable information regarding biological mechanisms, raises questions about the translatability of findings to human populations. Additionally, the evaluation of a limited time frame may not fully capture the long-term effects of hormonal and mechanical alterations on condylar morphology and health. Future research should consider longitudinal studies exploring different time points and the potential recovery mechanisms following hormonal restoration or mechanical intervention.

Conclusion

This study underscores the critical roles of estrogen and mechanical occlusal factors in the pathogenesis of idiopathic condylar resorption (ICR). Reduced serum estradiol levels, induced by hormonal manipulation and mechanical interference, resulted in harmful histopathological changes in condylar cartilage, including decreased thickness, disordered chondrocytes, and compromised trabecular bone integrity. The differential expression of estrogen receptors ERα and ERβ highlights the complex interaction between hormonal signaling and mechanical stressors. These findings emphasize the need for a comprehensive approach in managing TMJ disorders, addressing both hormonal and mechanical factors. Future research should focus on the long-term effects of these interactions and on developing effective therapeutic strategies to restore balance within the TMJ environment.

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Author Contributions

Jia Wang: Roles/Writing-original draft, Writing-review & editing. Pei Xu: Data curation. Huan Zhang: Validation. Chuan-jun Chen: Investigation.

Conflict of Interest

No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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