

# Similarities and differences of estrogen in the regulation of temporomandibular joint osteoarthritis and knee osteoarthritis

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**Summary.** Background. Temporomandibular joint osteoarthritis (TMJOA) and knee osteoarthritis (knee OA) are two kinds of common osteoarthritis (OA) that are characterized by chronic degeneration of soft and hard tissues around joints. Their gender and age differences suggest that there are similarities and differences between the pathogenic mechanisms of TMJOA and knee OA.

**Objective.** To review recent studies on the effect of estrogen on TMJOA and knee OA, and summarize their possible pathogenesis and molecular mechanisms.

**Sources.** Articles up to present reporting the relationship of estrogen and TMJOA or knee OA are included. An extensive electronic search was conducted of databases including PubMed, Web of science core collection.

**Conclusion.** According to epidemiological investigations, TMJOA primarily happens to females of puberty and childbearing age, while knee OA mainly affects postmenopausal women. Epidemiological investigation and experimental research suggest that estrogen may have a different effect on TMJ and on knee. Though estrogen regulates TMJOA and knee OA via estrogen-related receptors (ERR), their pathogenesis and pathway of estrogen regulation are different. To find out the accurate regulation of estrogen on TMJOA and knee OA, specific pathways and molecular mechanisms still need further exploration.

**Key words:** TMJOA, Knee OA, Estrogen, ERR, Inflammation, Cartilage

## Introduction

Osteoarthritis (OA) is a kind of arthritis characterized by chronic degeneration of soft and hard tissues around joints, which is often accompanied by cartilage degeneration, subchondral bone reconstruction, synovitis and joint pain (Wang et al., 2015; Alzahrani et al., 2020). As an important load-bearing joint, knee joint is the most common site of OA. Clinical manifestations are pain and limited movement of the joint. Temporomandibular joint (TMJ) is a common site of osteoarthritis (OA). TMJOA is a kind of degenerative joint disease, which is an important subtype of temporomandibular disorders (TMD) (Schiffman et al., 2014; Wang et al., 2015; Alzahrani et al., 2020).

TMJOA is a degenerative disease caused by an imbalance of TMJ homeostasis. Due to the loss and metabolic imbalance of chondrocytes, TMJOA causes progressive destruction of articular cartilage accompanied by subchondral bone destruction and synovial inflammation (Schiffman et al., 2014; Wang et al., 2015). The progressive destruction and severe abrasion of the condyle cause the ramus to shorten, leading to the retraction of the mandible and the anterior open bite, which seriously affects the patient's oral function and facial profile.

Since the etiology of TMJOA is complicated and unclear, few effective therapies are available. Reports on the prevalence of TMJOA have shown significant gender differences (Zhao and Ma, 2006; Zhao et al., 2011; Li et al., 2020). Its preponderance in women and early onset during reproductive years according to epidemiological

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research are totally different from the epidemiological characteristic of other joints such as knee OA, which primarily happens to postmenopausal women (Zhao et al., 2019; Dai et al., 2020). Considering estrogen is the primary factor determining female gender, and has been proved to play an important role in knee OA, the relationship between TMJOA and estrogen has attracted much attention. In this article, we summarize epidemiological reports on gender difference of TMJOA and knee OA, the specific effects of estrogen on TMJOA based on animal studies in recent years, and discuss possible mechanism underlying estrogen involvement in the regulation of TMJOA

### **Recent reports on gender and age differences of TMJOA and knee OA**

Reports show that knee OA occurs more frequently in elderly women, especially in perimenopausal and postmenopausal women. A retrospective study by Li D et al. showed that the average incidence of knee OA in Chinese females (19.1%) was significantly higher than that of male (10.9%). While the prevalence of knee OA increased with age in both sexes, the number of female cases increased more rapidly compared with males, especially after 40 years old (Li et al., 2020). The National Arthritis Data Workgroup of the United States reported the prevalence of OA in women over 45 (30.1%) was significantly higher than that in men (24.3%) in The National Health and Nutrition Examination Survey (Helmick et al., 2008).

There are also obvious gender differences in the incidence of TMJOA. Unlike knee OA, the highest prevalence of TMJOA occurs in women aged 20-40 (Warren and Fried, 2001), but TMJOA is more common in young women. According to the Investigation by Zhao YP et al., the frequency of TMJOA in patients aging 11 to 30 years was higher in women (563/3360, 16.8%) than in men (148/1523, 9.7%) (Zhao et al., 2011). Another investigation reports the detection rate of TMJOA among 10032 Chinese orthodontic patients from 1998 to 2003, showing a significant gender difference between women (134/6409, 2.1%) and men (37/3623, 1%) (Zhao and Ma, 2006). Adel Alzahrani et al. also reported a higher prevalence and severity of TMJOA in women than in men by assessing 145 randomly selected cone-beam computed tomography scans (Alzahrani et al., 2020). There are no large-scale epidemiological investigations about TMJOA. However, as mentioned above, existing clinical and retrospective studies have reported the gender and age differences of TMJOA, which may provide new ideas for studying the etiology and treatment of TMJOA.

In summary, according to related reports, the incidence of both types of OA in women is significantly higher than that in men. While in terms of age, the onset of TMJOA during reproductive years is different from knee OA that primarily afflicts postmenopausal women. The epidemiological characteristics may suggest that

estrogen may account for the gender diversity of OA in both joints, but there are similarities and differences between the pathogenic mechanisms of TMJOA and knee OA.

### **Estrogen may have a different effect on TMJ and on knee**

Considering that estrogen is the primary factor determining female gender, the relationship between OA and estrogen has attracted much attention. According to the recent articles, although views differ strongly on whether estrogen protects or damages cartilage, studies have shown that a reduction in estrogen levels has a damaging effect on knee cartilage (Sniekers et al., 2008). As for TMJOA, the effect of estrogen on it has not been clear. The regulation pathway and mechanism of estrogen on TMJOA may be different from that of knee OA.

Studies have shown that the serum estrogen levels of patients with knee OA are significantly lower than those without knee OA (Afzal and Khanam, 2011). Gao et al. studied the serum concentrations of estradiol and estrogen metabolites in women with or without knee OA, and found that the serum concentrations of free and total estrogen in postmenopausal women with OA was significantly decreased (Gao et al., 2010). Sniekers et al. reviewed studies describing the effect of OVX and estrogen treatment on animal models. 11 out of 14 studies shown OVX had a detrimental effect on cartilage, and 11 out of 22 animal studies reported estrogen had a beneficial effect on cartilage, most of which are carried out on the knee joint. The results above indicate considerable evidence for a relation between cartilage degeneration and estrogen (Sniekers et al., 2008).

However, the level of estrogen in patients with TMJOA is not exactly the same. Landi et al. tested the serum estrogen levels of patients with TMD (including TMJOA) and found that these levels were higher in male and female patients than in the normal-control group (Landi et al., 2005). Our previous studies also reported that estrogen can aggravate the progression of TMJOA in rats in a dose-dependent manner, and OVX can reduce this progression (Kou et al., 2011; Wang et al., 2013). However there are also reports that contradict this, showing that estrogen  $<10^{-8}$  mol/L can promote the synthesis of proteoglycan in chondrocytes (Cheng et al., 2003), and OVX can reduce the thickness of the TMJ condylar cartilage in female rats and that estrogen replacement therapy can alleviate it (Yasuoka et al., 2000). To compare the different effects that estrogen has on TMJ and knee, Y. Park et al. developed an OVX mouse model with estrogen levels similar to cycling women. And they found the administration of E2 resulted in a 40% to 50% reduction in TMJ fibrocartilage collagen and glycosaminoglycans (GAG) content but had no discernible effects on knee meniscus (KM) fibrocartilaginous matrices (Park et al., 2019).

As mentioned before, Estrogen might have a different effect on TMJ from that on knee, and the regulatory mechanism still needs to be discussed.

### **Possible mechanism underlying estrogen involvement in the regulation of TMJOA.**

#### *Estrogen regulates TMJOA and knee OA via estrogen-related receptors (ERR)*

Since receptors have been detected in human articular chondrocytes, the combination of estrogen and estrogen receptors might play a key role in estrogen's regulation of target organs (Sowers et al., 2006; Puri et al., 2009). Estrogen binds to the estrogen receptor, activates it, and causes it to bind to the estrogen response element in the promoter region of the target gene or to interact with other transcription factors (TFs) to regulate the expression of the target gene (Wang et al., 2009). Studies have shown that ERR are expressed in both TMJ and knee (Patel et al., 2018; Park et al., 2019). However, the cartilage of TMJ is fibrocartilage while the cartilage of knee joint is hyaline cartilage, which may be the reason that knee OA and TMJ OA respond differently to estrogen. There are obvious differences in histological origin between the two cartilage tissues. Hyaline cartilage of knee joint originates from the mesoderm, while fibrocartilage of TMJ originates from neural crest cells. Hyaline cartilage is mainly composed of type II collagen, and its matrix is rich in ground substance. On the other hand, fibrocartilage is mainly composed of collagen I, and its matrix is rich in densely braided collagen fibres. The different composition and structure give them different resistance to compression and molecular regulatory pathways, which may include the type and quantity of the ERR on their cartilage. Therefore, as mentioned above, the different effects of estrogen on the two joints may be related to the distribution of ERR and their different pathways.

Many experiments have proved that the mechanism of knee OA is mainly related to  $ERR\alpha$  and  $ERR\gamma$ . Studies have shown that inhibition of  $ERR\alpha$  expression can lead to inflammation and cartilage destruction in a postmenopausal OA rat model (Tian et al., 2019). However, overexpression of  $ERR\gamma$  in mouse knee joint cartilage can increase the expression of matrix metalloproteinases (MMPs), including MMP-3 and MMP-9, and then lead to OA (Son et al., 2017). Many studies have reported that selective estrogen receptor modulators (SERMs) or other estrogen-related drugs have significant effects on knee OA, suggesting estrogen may affect knee joint through ERR (Lugo et al., 2014; Xiao et al., 2016). Fig. 1 summarizes the possible ERR and down-stream regulation pathway of estrogen in knee OA (Tang et al., 2021).

However, ERR and related mechanisms of estrogen in TMJOA still need to be explored. Melissa Stemig et al. analyzed DNA samples from 42 DJD patients and 36 controls without DJD, and found that there was a higher

number of  $ERR\alpha$  genotypes in the DJD patients, suggesting that the presence of polymorphism possibly modulates the  $ERR\alpha$  activity in bone and contributes to the degenerative process in the joint (Stemig et al., 2015). In 8-week-old female rats, expression of  $ERR\alpha$  in condylar cartilage is higher than that in male rats of the same age (Yu et al., 2009). The level of  $ERR\alpha$  and  $ERR\beta$  and the ratio of  $ERR\alpha$  and  $ERR\beta$  in the mouse TMJ disc are significantly higher than in the knee meniscus, suggesting that this difference in expression might lead to corresponding downstream differences in gene expression and in turn affect the effect of estrogen on target organs (Wang et al., 2009). A recent study found that estradiol (E2) stimulation caused the loss of extracellular matrix (ECM) through the estrogen- $ERR\beta$ -HIF2 $\alpha$  pathway, and that these phenomena could be reversed by both pan-ER antagonist and HIF2 $\alpha$  translation inhibitor (Ye et al., 2020). Our previous study also showed that the ERR antagonist ICI 182780 partially blocked E2's promoting effects on TMJOA (Wang et al., 2013).

#### *Possible pathogenesis and pathway of estrogen regulation*

In the pathogenesis of OA, the metabolic imbalance of the ECM and the vascularization of cartilage are considered the main causes of matrix degradation (Tanaka et al., 2008). The main components of the cartilage dynamically balance between anabolism and catabolism. However, under the action of excessive physical stress and cytokines like interleukin (IL), the expression of matrix-degrading enzymes that degrade ECM such as MMPs, a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), and proangiogenic factors, is upregulated. Excessive catabolism causes loss of the ECM, which in turn leads to the destruction of cartilage and subchondral bone and the formation of OA (Ma et al., 2014; Shen et al., 2015; Ahmad et al., 2018; Ye et al., 2020). Studies have shown that high doses of estrogen can promote the expression of MMPs in condylar chondrocytes. Y. Park et al. found that, in an OVX mouse model, administration of E2 caused a significant loss of collagen and glycosaminoglycans both in TMJOA and knee OA, accompanied by amplification of  $ERR\alpha$  and specific increases in MMP9 and MMP13 expression (Park et al., 2019). However according to dose-response experiments TMJ fibrocartilaginous cells showed a greater sensitivity and a higher peak induction of MMP9 and MMP13 than knee meniscus cells to E2, providing an explanation for the differential responses of these tissues to E2 (Park et al., 2019). Zhao et al. used OA animal models to prove that  $ERR\gamma$  activates MMP9 and vascular endothelial growth factor A (VEGFA) through the extracellular signal-regulated kinase (ERK) signaling pathway, causing cartilage destruction in TMJ (Zhao et al., 2019). Inhibition of  $ERR\gamma$  expression, transcriptional activity, or both reduces the levels of MMP-3/9/13 and VEGFA

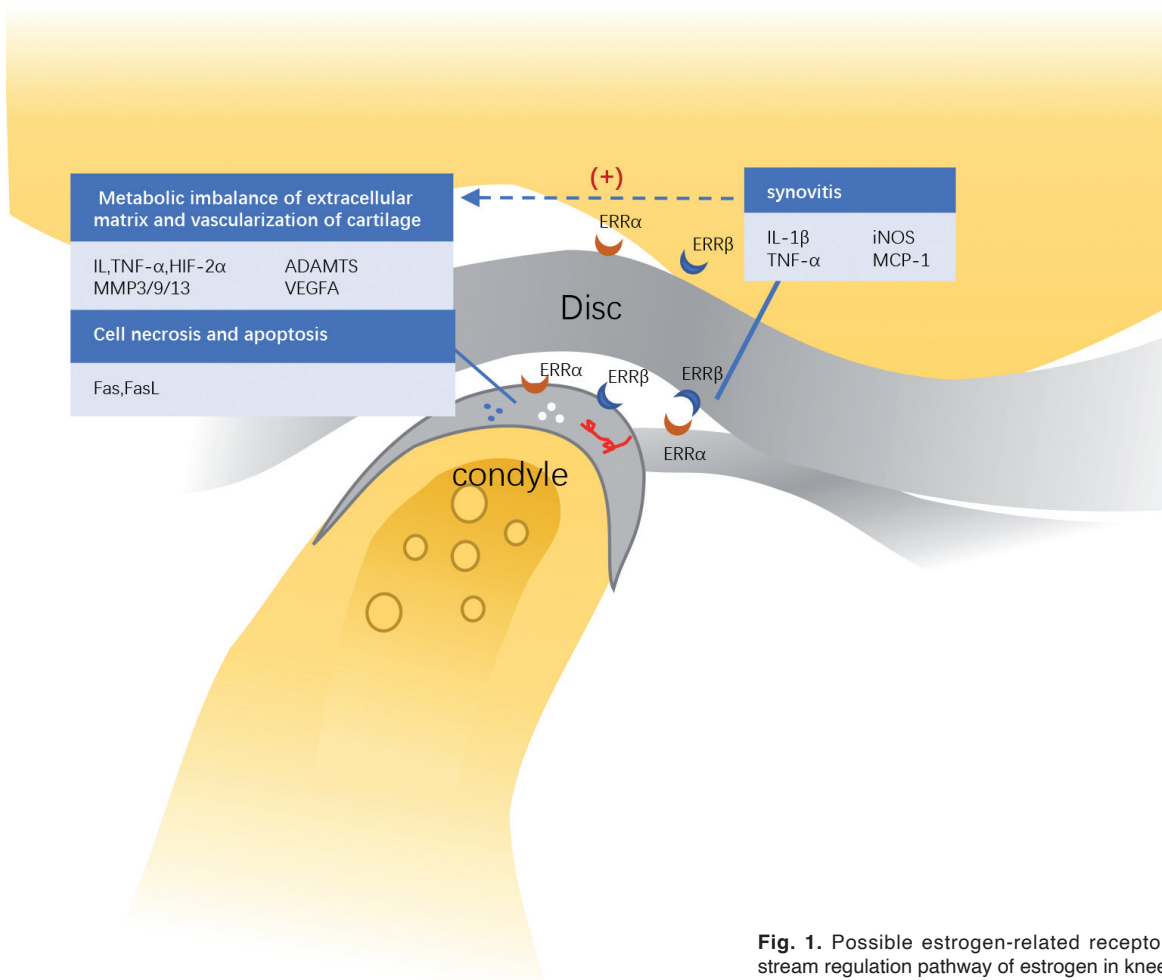
protein, thereby inhibiting angiogenesis and the degradation of ECM, and reducing the degree of cartilage destruction (Ma et al., 2014; Zhao et al., 2019). However, some studies report a protective effect of estrogen on TMJ cartilage. Robinson et al. found that, in mature mice, protease activity was partly inhibited by estrogen treatment via the upregulation and activity of protease inhibitor 15 (Pi15) and alpha-2-macroglobulin (A2m) (Robinson et al., 2018). Wu et al. using OVX mice in controlled experiments found that the combination of estrogen deficiency and excessive mechanical stress might aggravate TMJOA by activating the ERK pathway (Wu et al., 2019).

The progressive destruction of articular cartilage involves the loss of cartilage cells, which might be related to cell necrosis or apoptosis, and matrix degradation, which is mainly caused by metabolic imbalance in ECM (Wang et al., 2013; Choi et al., 2019). Some scholars believe that chondrocyte death, including apoptosis and cell necrosis, might play an important role in the progressive destruction of cartilage (Choi et al., 2019). Tamoxifen, an estrogen receptor substitute, can

induce apoptosis in chondrocytes of growth plate cultured in vitro, and increase the expression of both Fas, a death receptor family member, and FasL (Chagin et al., 2007). In addition, estrogen can upregulate the expression of FasL in osteoclasts, reduce bone resorption, and inhibit osteoporosis by promoting osteoclastic apoptosis, suggesting that estrogen could have a significant regulatory effect on Fas-related apoptosis signaling pathways (Nakamura et al., 2007). Our previous work showed that, in a monosodium iodoacetic acid (MIA)-induced rat TMJOA model, E2 enhanced the TMJOA in a dose-dependent manner by increasing proapoptotic genes and histological characterization of fibrocartilage degradation and bone erosion (Wang et al., 2013). Fig. 2 summarizes possible ERR, cytokines and regulation pathway of estrogen in TMJOA.

*Estrogen might regulate cartilage homeostasis through synovitis indirectly*

Many studies have proven that when cartilage



**Fig. 1.** Possible estrogen-related receptors(ERR) and downstream regulation pathway of estrogen in knee OA.



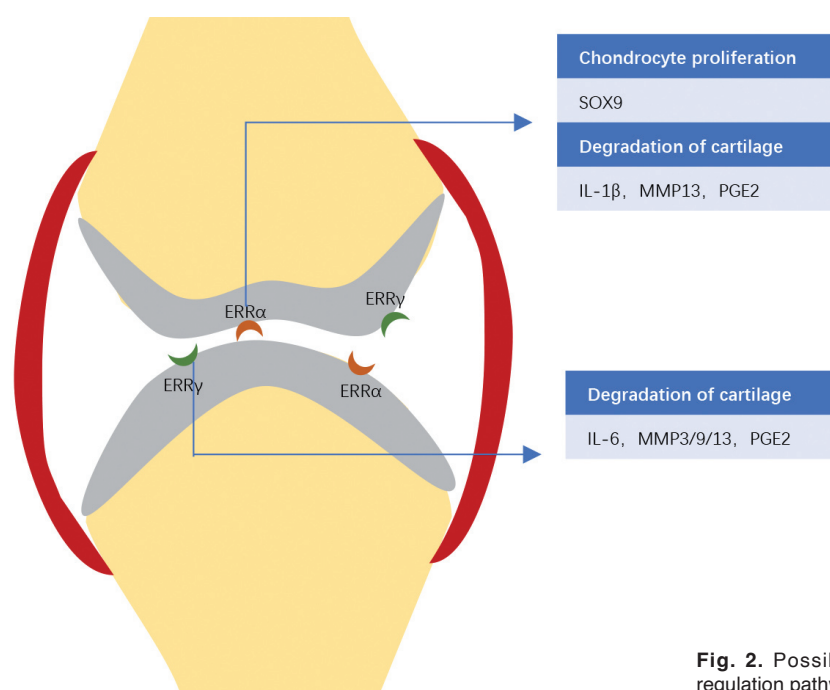
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presents typical signs of OA, the synovium also presents signs of chronic inflammation such as subsynovial tissue hyperplasia and monocyte infiltration (Xue et al., 2018). In recent years, there is increased attention to the role of synovial inflammation in OA. Studies have reported that for the joints like knee, synovium may play an important role in the OA (Bay-Jensen et al., 2010). Synovium may show significant changes, even before visible cartilage degeneration has occurred (Mathiessen and Conaghan, 2017). More and more evidence shows that synovitis and the resulting pro-inflammatory mediators such as cytokines, nitric oxide, prostaglandin E(2) and neuropeptides will destroy the balance of cartilage matrix degradation and repair, leading to excess production of the proteolytic enzymes responsible for cartilage breakdown (Sellam and Berenbaum, 2010; Mathiessen and Conaghan, 2017). These studies are mainly based on knee joints.

However, the role of synovium in TMJOA is still not very clear. Studies have shown that inflammatory factors such as tumor necrosis factor (TNF)- $\alpha$  and IL-1 $\beta$  are highly expressed in the synovial tissue of patients with OA, and that there is obvious monocyte infiltration in the synovium (Sellam and Berenbaum, 2010). Monocyte chemoattractant protein 1 (MCP-1) is also detected in fluids and in inflamed synovial tissues of TMJOA patients (Ogura et al., 2010). Animal experiments confirm that expression of inducible nitric oxide synthase (iNOS) and IL-1 $\beta$  is higher in the synovium of female TMJOA rats and MCP-1 around the synovium than that of their male counterparts, and the infiltration of iNOS and macrophages is more obvious (Nakamura

et al., 2007). In in vitro experiments, female rats primary cultured fibroblast-like synoviocytes (FLSs) are more sensitive to TNF $\alpha$  treatment than male rats, and OVX in female rats repressed such sensitivity due to the loss of estrogen production (Xue et al., 2018). However, no differences in the expression of ER $\alpha$  and ER $\beta$  were detected in female versus male synovial cells (Tsutsui et al., 2015; Xue et al., 2018). Studies have shown that estrogen is involved in the regulation of TMJ inflammation (Puri et al., 2009) Estrogen can aggravate complete Freund's adjuvant (CFA)-induced acute synovitis in rats by promoting nuclear translocation of nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells (NF- $\kappa$ B), and estrogen receptor blockers can reverse this effects (Kou et al., 2011). However, whether estrogen affects TMJOA by regulating synovitis needs further exploration.

A large number of studies have shown that estrogen is an important regulator of inflammation, but the underlying mechanism is very complicated, and the regulatory effect varies greatly by target organ (Straub, 2007). As a pivotal enzyme for survival and health in both genders, estrogen plays an important role in systemic changes and disease. Abnormal estrogen fluctuations may cause tissue degeneration (bone, muscle, neural etc.), and metabolite imbalance (glucose, lipid etc.) (Simpson et al., 2002). Excess estrogen can lead to an overexpression of estrogen receptors (ERR $\alpha$  and ERR $\beta$ ), harming tissues, leading to autoimmune diseases, and neoplasms (Patel et al., 2018). Though the cause of osteoarthritis is not yet fully understood, complex interplay of constitutional, genetic



**Fig. 2.** Possible estrogen-related receptors(ERR), cytokines and regulation pathway of estrogen in TMJOA.

predisposition, cellular, and biochemical processes are currently being considered closely related to the occurrence of OA (Roos and Arden, 2016; Lespasio et al., 2017). And the above factors are often related to systemic diseases. Although studies have shown that estrogen has a role in the pathogenesis of knee OA, and hormone replacement therapy (HRT) may inhibit the progression and occurrence of knee OA (Driban et al., 2016), whether this effect is direct or through other factors such as obesity and inflammation is still unknown (Hussain et al., 2018). Studies have shown an increased health risk after HRT, suggesting that the effect of estrogen on systemic changes of OA patients need more attention (Rossouw et al., 2007). Though few studies about the effects of estrogen on the systemic response of patients of TMJOA have been published, exploring what role estrogen plays in this process may help find some clues for the study of TMJOA.

In summary, studies in recent years have shown that estrogen may regulate TMJOA via ERR on condyle cartilage and down-stream OA-related cytokines. Different composition and sensitivity of ERR on fibrocartilaginous cells may lead to the difference that estrogen shows on TMJOA and knee OA. Synovium may also play an important role in the development of TMJOA. However, the specific pathways and molecular mechanisms still need further exploration.

## Summary

As two important synovial joints of our body, the prevalence of knee OA and TMJOA has been proved closely related to females. According to epidemiological investigations, females of puberty and childbearing age are more susceptible to TMJOA, while knee OA mainly affects postmenopausal women. By searching recent articles, we overview epidemiological evidence and experiments to prompt that estrogen may play a different role in the development of these two kinds of OA. Estrogen and related preparations have been experimentally confirmed to have some effect on knee OA (Xiao et al., 2016; Xu et al., 2019), and we hope this article could be helpful for the mechanism research and treatment therapy of TMJOA in the future by summarizing the possible mechanisms of estrogen in the regulation of TMJOA.

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## References

- Ahmad N., Chen S., Wang W. and Kapila S. (2018). 17beta-estradiol induces mmp-9 and mmp-13 in tmj fibrochondrocytes via estrogen receptor alpha. *J. Dent. Res.* 97, 1023-1030.
- Alzahrani A., Yadav S., Gandhi V., Lurie A.G. and Tadinada A. (2020). Incidental findings of temporomandibular joint osteoarthritis and its variability based on age and sex. *Imaging Sci. Dent.* 50, 245-253.
- Bay-Jensen A.C., Hoegh-Madsen S., Dam E., Henriksen K., Sondergaard B.C., Pastoureaux P., Qvist P. and Karsdal M.A. (2010). Which elements are involved in reversible and irreversible cartilage degradation in osteoarthritis?. *Rheumatol. Int.* 30, 435-442.
- Chagin A.S., Karimian E., Zaman F., Takigawa M., Chrysis D. and Savendahl L. (2007). Tamoxifen induces permanent growth arrest through selective induction of apoptosis in growth plate chondrocytes in cultured rat metatarsal bones. *Bone* 40, 1415-1424.
- Cheng P., Ma X., Xue Y., Li S. and Zhang Z. (2003). Effects of estradiol on proliferation and metabolism of rabbit mandibular condylar cartilage cells *in vitro*. *Chin. Med. J. (Engl.)* 116, 1413-1417.
- Choi M.C., Jo J., Park J., Kang H.K. and Park Y. (2019). Nf-kappab signaling pathways in osteoarthritic cartilage destruction. *Cells* 8, 734.
- Dai X., Ying P., Ding W., Li H., Xu P., Huang Z., Zhang N. and Liu J. (2020). Genetic estrogen receptor alpha gene Pvuii polymorphism in susceptibility to knee osteoarthritis in a chinese han population: A southern jiangsu study. *Knee* 27, 803-808.
- Driban J.B., Lo G.H., Eaton C.B., Lapane K.L., Nevitt M., Harvey W.F., McCulloch C.E. and McAlindon T.E. (2016). Exploratory analysis of osteoarthritis progression among medication users: Data from the osteoarthritis initiative. *Ther. Adv. Musculoskelet. Dis.* 8, 207-219.
- Gao W., Zeng C., Cai D., Liu B., Li Y., Wen X. and Chen Y. (2010). Serum concentrations of selected endogenous estrogen and estrogen metabolites in pre- and post-menopausal chinese women with osteoarthritis. *J. Endocrinol. Invest.* 33, 644-649.
- Helmick C.G., Felson D.T., Lawrence R.C., Gabriel S., Hirsch R., Kwoh C.K., Liang M.H., Kremers H.M., Mayes M.D., Merkel P.A., Pillemer S.R., Reveille J.D., Stone J.H. and National Arthritis Data W. (2008). Estimates of the prevalence of arthritis and other rheumatic conditions in the united states. Part I. *Arthritis Rheum.* 58, 15-25.
- Hussain S.M., Cicuttini F.M., Alyousef B. and Wang Y. (2018). Female hormonal factors and osteoarthritis of the knee, hip and hand: A narrative review. *Climacteric* 21, 132-139.
- Kou X.X., Wu Y.W., Ding Y., Hao T., Bi R.Y., Gan Y.H. and Ma X. (2011). 17beta-estradiol aggravates temporomandibular joint inflammation through the nf-kappab pathway in ovariectomized rats. *Arthritis Rheum.* 63, 1888-1897.
- Landi N., Lombardi I., Manfredini D., Casarosa E., Biondi K., Gabbanini M. and Bosco M. (2005). Sexual hormone serum levels and temporomandibular disorders. A preliminary study. *Gynecol. Endocrinol.* 20, 99-103.
- Lespasio M.J., Piuzzi N.S., Husni M.E., Muschler G.F., Guarino A. and Mont M.A. (2017). Knee osteoarthritis: A primer. *Perm. J.* 21, 16-183.
- Li D., Li S., Chen Q. and Xie X. (2020). The prevalence of symptomatic knee osteoarthritis in relation to age, sex, area, region, and body mass index in china: A systematic review and meta-analysis. *Front Med. (Lausanne)* 7, 304.
- Lugo L., Villalvilla A., Largo R., Herrero-Beaumont G. and Roman-Blas J.A. (2014). Selective estrogen receptor modulators (serms): New
- Afzal S. and Khanam A. (2011). Serum estrogen and interleukin-6 levels

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- alternatives for osteoarthritis?. *Maturitas* 77, 380-384.
- Ma C., Wu G., Wang Z., Wang P., Wu L., Zhu G. and Zhao H. (2014). Effects of chronic sleep deprivation on the extracellular signal-regulated kinase pathway in the temporomandibular joint of rats. *PLoS One* 9, e107544.
- Mathiessen A. and Conaghan P.G. (2017). Synovitis in osteoarthritis: Current understanding with therapeutic implications. *Arthritis Res. Ther.* 19, 18.
- Nakamura T., Imai Y., Matsumoto T., Sato S., Takeuchi K., Igarashi K., Harada Y., Azuma Y., Krust A., Yamamoto Y., Nishina H., Takeda S., Takayanagi H., Metzger D., Kanno J., Takaoka K., Martin T.J., Chambon P. and Kato S. (2007). Estrogen prevents bone loss via estrogen receptor alpha and induction of fas ligand in osteoclasts. *Cell* 130, 811-823.
- Ogura N., Satoh K., Akutsu M., Tobe M., Kuyama K., Kuboyama N., Sakamaki H., Kujiraoka H. and Kondoh T. (2010). MCP-1 production in temporomandibular joint inflammation. *J. Dent. Res.* 89, 1117-1122.
- Park Y., Chen S., Ahmad N., Hayami T. and Kapila S. (2019). Estrogen selectively enhances tmj disc but not knee meniscus matrix loss. *J. Dent. Res.* 98, 1532-1538.
- Patel S., Homaei A., Raju A.B. and Meher B.R. (2018). Estrogen: The necessary evil for human health, and ways to tame it. *Biomed. Pharmacother.* 102, 403-411.
- Puri J., Hutchins B., Bellinger L.L. and Kramer P.R. (2009). Estrogen and inflammation modulate estrogen receptor alpha expression in specific tissues of the temporomandibular joint. *Reprod. Biol. Endocrinol.* 7, 155.
- Robinson J.L., Soria P., Xu M., Vrana M., Luchetti J., Lu H.H., Chen J. and Wadhwa S. (2018). Estrogen promotes mandibular condylar fibrocartilage chondrogenesis and inhibits degeneration via estrogen receptor alpha in female mice. *Sci. Rep.* 8, 8527.
- Roos E.M. and Arden N.K. (2016). Strategies for the prevention of knee osteoarthritis. *Nat. Rev. Rheumatol.* 12, 92-101.
- Rossouw J.E., Prentice R.L., Manson J.E., Wu L., Barad D., Barnabei V.M., Ko M., LaCroix A.Z., Margolis K.L. and Stefanick M.L. (2007). Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 297, 1465-1477.
- Schiffman E., Ohrbach R., Truelove E., Look J., Anderson G., Goulet J.P., List T., Svensson P., Gonzalez Y., Lobbezoo F., Michelotti A., Brooks S.L., Ceusters W., Drangsholt M., Ettlin D., Gaul C., Goldberg L.J., Haythornthwaite J.A., Hollender L., Jensen R., John M.T., De Laat A., de Leeuw R., Maixner W., van der Meulen M., Murray G.M., Nixdorf D.R., Palla S., Petersson A., Pionchon P., Smith B., Visscher C.M., Zakrzewska J., Dworkin S.F., International Rdc/Tmd Consortium Network I.a.f.d.R. and Orofacial Pain Special Interest Group I.A.f.t.S.o.P. (2014). 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 groupdagger. *J. Oral Facial Pain Headache* 28, 6-27.
- Sellam J. and Berenbaum F. (2010). The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. *Nat. Rev. Rheumatol.* 6, 625-635.
- Shen P., Jiao Z., Zheng J.S., Xu W.F., Zhang S.Y., Qin A. and Yang C. (2015). Injecting vascular endothelial growth factor into the temporomandibular joint induces osteoarthritis in mice. *Sci. Rep.* 5, 16244.
- Simpson E.R., Clyne C., Rubin G., Boon W.C., Robertson K., Britt K., Speed C. and Jones M. (2002). Aromatase--a brief overview. *Annu. Rev. Physiol.* 64, 93-127.
- Sniekers Y.H., Weinans H., Bierma-Zeinstra S.M., van Leeuwen J.P. and van Osch G.J. (2008). Animal models for osteoarthritis: The effect of ovariectomy and estrogen treatment - a systematic approach. *Osteoarthritis Cartilage* 16, 533-541.
- Son Y.O., Park S., Kwak J.S., Won Y., Choi W.S., Rhee J., Chun C.H., Ryu J.H., Kim D.K., Choi H.S. and Chun J.S. (2017). Estrogen-related receptor gamma causes osteoarthritis by upregulating extracellular matrix-degrading enzymes. *Nat. Commun.* 8, 2133.
- Sowers M.R., McConnell D., Jannausch M., Buyuktur A.G., Hochberg M. and Jamadar D.A. (2006). Estradiol and its metabolites and their association with knee osteoarthritis. *Arthritis Rheum.* 54, 2481-2487.
- Stemig M., Myers S.L., Kaimal S. and Islam M.S. (2015). Estrogen receptor-alpha polymorphism in patients with and without degenerative disease of the temporomandibular joint. *Cranio* 33, 129-133.
- Straub R.H. (2007). The complex role of estrogens in inflammation. *Endocr. Rev.* 28, 521-574.
- Tanaka E., Detamore M.S. and Mercuri L.G. (2008). Degenerative disorders of the temporomandibular joint: Etiology, diagnosis, and treatment. *J. Dent. Res.* 87, 296-307.
- Tang J.S., Liu T., Wen X.G., Zhou Z.S., Yan J.T., Gao J.P. and Zuo J.L. (2021). Estrogen-related receptors: Novel potential regulators of osteoarthritis pathogenesis. *Mol. Med.* 27, 5.
- Tian L., Su Z., Ma X., Wang F. and Guo Y. (2019). Inhibition of miR-203 ameliorates osteoarthritis cartilage degradation in the postmenopausal rat model: Involvement of estrogen receptor alpha. *Hum. Gene Ther. Clin. Dev.* 30, 160-168.
- Tsutsui H., Cai X. and Hayashi S. (2015). Interleukin-1 family cytokines in liver diseases. *Mediators Inflamm.* 2015, 630265.
- Wang W., Hayami T. and Kapila S. (2009). Female hormone receptors are differentially expressed in mouse fibrocartilages. *Osteoarthritis Cartilage* 17, 646-654.
- Wang X.D., Kou X.X., Meng Z., Bi R.Y., Liu Y., Zhang J.N., Zhou Y.H. and Gan Y.H. (2013). Estrogen aggravates iodoacetate-induced temporomandibular joint osteoarthritis. *J. Dent. Res.* 92, 918-924.
- Wang X.D., Zhang J.N., Gan Y.H. and Zhou Y.H. (2015). Current understanding of pathogenesis and treatment of tmj osteoarthritis. *J. Dent. Res.* 94, 666-673.
- Warren M.P. and Fried J.L. (2001). Temporomandibular disorders and hormones in women. *Cells Tissues Organs* 169, 187-192.
- Wu Y., Kadota-Watanabe C., Ogawa T. and Moriyama K. (2019). Combination of estrogen deficiency and excessive mechanical stress aggravates temporomandibular joint osteoarthritis *in vivo*. *Arch. Oral Biol.* 102, 39-46.
- Xiao Y.P., Tian F.M., Dai M.W., Wang W.Y., Shao L.T. and Zhang L. (2016). Are estrogen-related drugs new alternatives for the management of osteoarthritis?. *Arthritis Res. Ther.* 18, 151.
- Xu X., Li X., Liang Y., Ou Y., Huang J., Xiong J., Duan L. and Wang D. (2019). Estrogen modulates cartilage and subchondral bone remodeling in an ovariectomized rat model of postmenopausal osteoarthritis. *Med. Sci. Monit.* 25, 3146-3153.
- Xue X.T., Zhang T., Cui S.J., He D.Q., Wang X.D., Yang R.L., Liu D.W., Liu Y., Gan Y.H., Kou X.X. and Zhou Y.H. (2018). Sexual dimorphism of estrogen-sensitized synoviocytes contributes to gender difference in temporomandibular joint osteoarthritis. *Oral Dis.* 24, 1503-1513.
- Yasuoka T., Nakashima M., Okuda T. and Tatematsu N. (2000). Effect

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- of estrogen replacement on temporomandibular joint remodeling in ovariectomized rats. *J. Oral Maxillofac. Surg.* 58, 189-196; discussion 196-187.
- Ye T., He F., Lu L., Miao H., Sun D., Zhang M., Yang H., Zhang J., Qiu J., Zhao H., Ma Z. and Yu S. (2020). The effect of oestrogen on mandibular condylar cartilage via hypoxia-inducible factor-2alpha during osteoarthritis development. *Bone* 130, 115123.
- Yu S.B., Wang M.Q., Li Y.Q., Lv X., Jiang Y., Dong G.Y. and Ma Z.F. (2009). The effects of age and sex on the expression of oestrogen and its receptors in rat mandibular condylar cartilages. *Arch. Oral Biol.* 54, 479-485.
- Zhao Y.P. and Ma X.C. (2006). [temporomandibular disorders related pain interaction with age, sex and imaging changes of osteoarthritis]. *Zhonghua Kou Qiang Yi Xue Za Zhi* 41, 757-758.
- Zhao Y.P., Zhang Z.Y., Wu Y.T., Zhang W.L. and Ma X.C. (2011). Investigation of the clinical and radiographic features of osteoarthritis of the temporomandibular joints in adolescents and young adults. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* 111, e27-34.
- Zhao H., Liu S., Ma C., Ma S., Chen G., Yuan L., Chen L. and Zhao H. (2019). Estrogen-related receptor gamma induces angiogenesis and extracellular matrix degradation of temporomandibular joint osteoarthritis in rats. *Front. Pharmacol.* 10, 1290.

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