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Estrogen signaling impacts temporomandibular joint and periodontal disease pathology

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Abstract

Women experience a higher incidence of oral diseases including periodontal diseases and temporomandibular joint disease (TMD) implicating the role of estrogen signaling in disease pathology. Fluctuating levels of estrogen during childbearing age potentiates facial pain, high estrogen levels during pregnancy promote gingivitis, and low levels of estrogen during menopause predisposes the TMJ to degeneration and increases alveolar bone loss. In this review, an overview of estrogen signaling pathways in vitro and in vivo that regulate pregnancy-related gingivitis, TMJ homeostasis, and alveolar bone remodeling is provided. Deciphering the specific estrogen signaling pathways for individual oral diseases is crucial for potential new drug therapies to promote and maintain healthy tissue.

Keywords

Estrogen; Temporomandibular joint; Periodontal disease; Alveolar bone; Oral health; Women's health

Introduction

Oral diseases are a major health burden worldwide and exhibit a large socio-economic impact [1]. Focused analyses on women's health have revealed sex dimorphisms in many oral health diseases. Temporomandibular joint disease (TMD), pregnancy-related gingivitis and age-related alveolar bone loss are all examples of diseases that are more common in women than in men [2, 3]. While this is a complex problem with many confounding factors,

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one possible mechanism for the increased prevalence of the diseases in women is due to differences in estrogen levels and corresponding signaling mechanisms.

Estrogen is crucial for development and homeostasis for both sexes even though relative levels vary. Physiological estrogen is found in three forms: estradiol, estrone, and estriol. Estradiol is the most potent and abundant form during the reproductive years, and most often used for in vitro and in vivo studies. In general, standardizing estrogen levels is difficult due to daily fluctuations in concentration and anatomical differences in the source. In men, low, constant levels of estrogen are present after puberty through the age of 60. The mean bioavailable estradiol (E2) is 13 pg/ml in men ages 20–30, 12 pg/ml in men 40–59 years of age and 8 pg/ml in men over the age of 60 [4]. In contrast, estradiol levels fluctuate from 5 pg/ml at the early follicular phase to a peak of 200–500 pg/ml just before ovulation in women of childbearing age. After menopause, the level of estradiol precipitously drops and remains constant around 3 pg/ml in women over the age of 60 [5]. As such, it is plausible that fluctuations in estrogen and corresponding changes in other sex hormones including progesterone and relaxin play a significant role on the pathogenesis and propagation of many oral health diseases. Sex differences in estradiol concentration in people 16–45 years of age have been implicated in gingivitis and TMD. Further, menopausal women are more likely than age-matched men to develop TMJ degeneration disease (TMJ-DD) and age-related alveolar bone loss. This review will provide a thorough evaluation of estrogen signaling at the cell and tissue level, sex dimorphism of TMD, gingivitis, and periodontal diseases, and provide target areas for future research.

Estrogen and TMD

Chronic TMD, including TMJ degenerative disease, is defined as pain in the TMJ area for at least 6 months [6]. Women are roughly three times more likely than men to develop chronic TMD [7–10]. The Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study, a large prospective clinical trial that investigated the natural history of acute and chronic TMD diseases, illustrated that only the chronic form of TMD predominantly afflicted women, whereas the acute form had equal prevalence between the sexes [11]. Likely, the increased prevalence of TMD found in women in a number of cross-sectional studies is due to the increased duration of TMD symptoms in women such that at any given time point, more women than men have TMJ symptoms [12].

Data on the effects of estrogen on TMD, however, are contradictory. Older studies demonstrated that TMD predominantly afflicted women of childbearing age, suggesting that higher estrogen levels potentiated the disease [8, 13]. However, recent studies in Europe and the US with larger patient samples sizes have shown that the prevalence for TMD peaks between 45 and 64 years of age and then gradually decreases [14, 15]. In the US study, TMD prevalence peaked at around 6% in 35–64 year olds and then decreased to 4% in 65–84 year olds; while in the European study, TMD prevalence peaked at 9% in 40–49 year old and then gradually decreased to 4% in 70–90 year old. Since the menopause transition and subsequent drop in estrogen levels occurs at age 45–55, these results suggest that low levels of estrogen may potentiate certain types of TMD. TMD comprises over 12 different diseases, making it difficult to differentiate the mechanistic role of estrogen in mediating one

of the many disease forms [16]. For example, in a recent study characterizing myalgia, disc disorders, and TMJ degeneration, it was determined that TMJ degeneration increased in women over the age of 50; whereas, disc disorders decreased in the same age group and peaked in women of childbearing age [17]. Another confounding variable is the reduction in bone quality due to osteoporosis, which is associated with bone loss in the oral region including the TMJ. However, the role of osteoporosis and TMJ bone changes is controversial with conflicting results on correlation between systemic bone loss and subchondral bone changes [18–20]. Taken together, the studies suggest that estrogen may have a biphasic effect on TMD with high and/or fluctuating levels promoting certain types of TMD and with low levels potentiating other types of TMD.

One way to examine the role of estrogen in mediating TMD is to examine its prevalence in post-menopausal women on hormone replacement therapy (HRT). Currently, four studies have investigated the effects of HRT on all TMD diseases. In the first study, a significant increase in TMD prevalence in post-menopausal women on HRT was observed [9]. However, at the time when the study was done, a large percentage of the post-menopausal women on HRT had undergone a hysterectomy [21]. This procedure can also result in increased TMD prevalence because of intubation [22], potentially biasing the results. In contrast, three recent studies found no significant difference in the prevalence of TMD in post-menopausal women on HRT compared to no treatment [23–25]. Taken together, the aforementioned studies suggest that hormone replacement may have no significant effect on the prevalence of TMD diseases overall.

Other recent studies have shown that TMD pain is reduced when estrogen levels are high. During pregnancy, there is a dramatic increase in estrogen levels. In one study, prevalence of TMD was 2–3 lower in pregnant versus nonpregnant age-matched females [26]. Further, in two longitudinal studies it was shown that reported orofacial pain diminished significantly during the third trimester of pregnancy [27] and increased post-partum [28], suggesting that TMD-related pain is reduced at high estrogen levels. One possible explanation for discordant results between pregnancy and hormone replacement is an altered sensitivity of tissue to fluctuating estrogen levels, rather than low or high concentrations [29].

The role of estrogen on TMJ structures

In humans, the temporomandibular joint is a bilateral diarthrodial joint, subjected to both hinge (inferior joint space) and sliding (both joint spaces) forces [30]. The complex mechanical functions of the TMJ are achieved by a biconcave fibrocartilaginous disc and articular fibrocartilage that cover the mandibular condyle and the articular surfaces of the temporal bone. During joint movement, the disc glides along the glenoid fossa and articular eminence [31]. The disc is divided into the anterior band, posterior band, and intermediate zone [32]. The intermediate zone is further subdivided into the lateral, central, and medial regions each of which exhibit different properties. Collagen fibers (mainly type I with trace amounts of type II) compose approximately 90% of the dry weight [33, 34], form a ring-like alignment around the periphery of the disc and are aligned in the anteroposterior direction [35, 36]. The disc matrix is comprised of approximately 5% proteoglycans. Chondroitin sulfate and dermatan sulfate make up the majority of the glycosaminoglycans (GAG) chains

on the proteoglycan proteins [33, 37–39]. Cell populations in the disc are heterogeneous with 70% fibroblast-like fibrochondrocytes throughout the tissue and 30% chondrocyte-like fibrochondrocytes localized in the intermediate zone [40, 41]. Biomechanical analysis of aged human TMJ discs illustrated an increase in overall stiffness and a reduction in relaxation after strain in female compared to male tissue [42]. Further, fixed charge density, the contribution of charged GAGs to the disc's ability to support load via osmotic pressure, was determined to be lower in aged female human discs compared to males [43]. This human data points to sex differences in extracellular matrix ultrastructure and contributing changes in mechanical properties, likely regulated by sex hormone signaling.

Similar to the disc, the mandibular condylar fibrocartilage is comprised of both collagen type 1 and 2. However, these tissues differ in the organization and composition of this matrix and the cells that interact and remodel the tissue. There are four zones of the articular fibrocartilage. The superficial zone contains cells that express lubricin. The second zone is the polymorphic zone that contains mesenchymal progenitors that are actively proliferating is response to stimuli. The third zone is the flattened zone and contains cells that express collagen type 2 (Col2). The fourth zone is the hypertrophic zone where mandibular condylar fibrocartilage cells undergo terminal maturation [44] and/or directly transform into osteocytes [45]. There are a finite number of progenitor cells in the superficial and polymorphic zones of the mandibular condylar fibrocartilage. Once these cells are depleted, growth ceases and the TMJ undergoes degenerative changes. Unlike long bone growth plate cartilages, the TMJ undergoes age-related changes. In humans at 15–30 years of age and in mice at 3–6 months of age, there is a decrease in TMJ growth, a progressive chondrogenesis of the superficial and polymorphic zone and disappearance of the hypertrophic zone [46, 47]. After these ages, there is cessation of growth, followed by a progressive decrease in mandibular condylar fibrocartilage cellularity and a gradual increase in degeneration that plateaus at 50–60 years of age in humans [46] and at 18 months of age in mice [47, 48].

Effects of estrogen on the TMJ disc

In vitro studies isolating the effects of estrogen treatment on single cell populations is one method to determine mechanisms of action during estradiol treatment. Table 1 includes a compilation of estrogen effects on TMJ disc and articular fibrocartilage. In baboon disc fibrochondrocytes, 10 nM estradiol treatment reduced the promoter activity and gene expression of proteoglycan 4 (Prg4), an important macro-molecule required for lubrication of the joint [49]. Further, estrogen in conjunction with relaxin increased both collagenase-1 and stromelysin-1 in rabbit in fibrochondrocyte cultures [50] and organ cultures [51]. Interestingly, estradiol had no significant effect on collagenase and stromelysin expression and activity on TMJ synoviocytes [50]. Although there are only a small number of studies investigating the effect of estrogen on the TMJ disc fibrochondrocytes in vitro, the data suggest that high levels of estradiol increase protease activity and decrease the production of ECM components that promote a healthy disc.

Gonadectomy, including ovariectomy for females and orchiectomy for males, is the standard animal model to determine estrogen effects on tissue. The TMJ disc from female rats ovariectomized and then treated with estradiol, relaxin, or progesterone were characterized

for total GAG and collagen content. Overall, estradiol and relaxin, alone and synergistically, reduced overall GAG and collagen content. However, when progesterone was administered on its own or in concert with estradiol and/or relaxin, GAG and collagen levels were not significantly different compared to the ovariectomized and sham controls [52]. While both in vitro and in vivo studies suggest estradiol reduces the production of ECM macromolecules, a larger set of experiments is required to validate these results.

Effects of estrogen on the mandibular condylar fibrocartilage

The health and function of the articular condylar fibrocartilage are necessary to withstand and redistribute the load on the subchondral bone. As such, damage to this fibrocartilage can lead to TMJ degeneration. In an organ culture model, estradiol decreased the articular fibrocartilage thickness and cell proliferation while increasing collagen type 10 in the hypertrophic chondrocyte zone [53]. Further, 10 nM estradiol decreased fibrochondrocytes' proliferation harvested from rat mandibular condyles. In rabbit mandibular condylar fibrochondrocytes, estradiol treatment increased cell proliferation and proteoglycan synthesis through 10^{-8} M after which estradiol reduced proliferation and proteogly can synthesis [54].

In vivo studies have shown that estradiol treatment increased the articular fibrocartilage thickness and subchondral bone volume after a week of treatment post ovariectomy in female Wistar rats [55]. On the other hand, in ovariectomized C57 female mice, estradiol decreased progenitor cell proliferation and fibrocartilage thickness compared to placebo treatment [56, 57]. These results were validated in 3-month old female rats in which estradiol treatment after ovariectomy (OVX), respectively, decreased progenitor cell proliferation and fibrocartilage thickness, specifically the hypertrophic layer [58]. Further, estradiol treatment increased interleukin 6 (IL6) concentration in female, OVX tissue compared to the vehicle control. While important to conduct in vitro studies to determine the specific cells responsible for the estrogen-induced effects, it is difficult to compare results with in vivo as the fibrochondrocytes are cultured in 2D on rigid, polystyrene culture dishes and passaged in these conditions, greatly affecting their phenotype [59, 60].

Estrogen signaling via nuclear estrogen receptors in TMJ

There are two distinct types of estrogen signaling mechanisms, genomic and non-genomic. In the genomic pathway, estrogen binds to estrogen receptor alpha (ERα) or beta (ERβ), inducing a conformational change in the receptors that cause dissociation from chaperones, dimerization, translocation into the nucleus, and activation of the receptor transcriptional domain [61]. In addition to the nuclear ERs, plasma membrane-associated ERs mediate the non-genomic signaling pathway that can lead both to cytoplasmic alterations and to regulation of gene expression [62]. Further, ERs, either dependently or independently of ligand binding, interact with other transcriptional pathways through protein–protein interactions likely involving phosphorylation modifications [63, 64]. Foundational studies in 1987 illustrated the sexual dimorphism in expression estrogen receptors (ER) in the TMJ using a baboon model [65]. Since then, a couple of studies have investigated the relative expression of ERα and ERβ in female rodents compared to males with mixed reviews. One study found higher expression of both receptors in fibrochondrocytes isolated from female

mouse TMJ; however, these cells were cultured for 4–6 passages likely altering their phenotype and gene expression [66]. Another study found that male rat TMJ tissue contained higher amounts of both receptors [67].

Overall, there are limited data detailing the role of ERα and ERβ in the TMJ. In the disc, studies have shown that increasing estradiol concentrations elevated MMP-9 and MMP-13 levels in TMJ disc fibrochondrocytes harvested from 12-week old female [68]. In both loss-of-function and gain-of-function studies, the increased MMP levels with estradiol were modulated via ERα signaling, with ERβ having an insignificant role. The effect of estrogen via ERα on mandibular condylar fibrocartilage morphology, matrix production, and protease activity was assessed in 7 and 17-week old mice. In the young mice, estrogen via ERα promoted mandibular condylar fibrocartilage chondrogenesis partly by inhibiting the canonical Wnt signaling pathway through upregulation of sclerostin (Sost). In the mature mice, protease activity was partly inhibited with estrogen treatment via the upregulation and activity of protease inhibitor 15 (Pi15) and alpha-2-macroglobulin (A2m) [57]. In male mice, estradiol via ERα mediates mandibular condylar fibrocartilage growth and maturation in young male mice using global ERαKO models [69]. In the same study, there was no significant evidence to suggest that ERα played a major role in age-related TMJ growth and/or degeneration in older mice. Further in mandibular condylar bone, estrogen effects of mandibular bone density were dependent on ERα nuclear signaling and did not require ERβ signaling [70]. Figure 1 provides a summary of the general effects of estrogen on the disc and condylar fibrocartilage.

While ERα mediates the majority of estrogen's transcriptional activity, ERβ plays a role in the sex differences observed in response to estrogen signaling. In young female mice, ERβ inhibits proliferation and ERα expression but does not play a role in estrogen-induced increase in anabolic gene expression including sclerostin (Sost) and collagen type 2 (Col2) [56], effects observed to be controlled via ERα [57]. Further, ERβ inhibits mandibular condyle growth by promoting fibrocartilage turnover [71]. On the other hand, ERβ does not play a significant role on the young male mandibular condylar fibrocartilage [72]. Based on these data, future studies focused on the targeted role of ER agonists and/or antagonists to control cell proliferation and matrix production are warranted.

Role of estrogen in animal models of TMJ degenerative disease (TMJ–DD)

Many TMJ-DD models have been employed to assess estradiol's effect in the diseased condition. There are three main classes of experimental TMJ-DD models: mechanical, chemical, and genetic. Unilateral anterior crossbite (UAC) is an acceptable mechanical model that results in degenerative changes to the mandibular condylar fibrocartilage and subchondral bone including decreased fibrocartilage thickness, reduced extracellular matrix, increased apoptosis and pro-inflammatory markers, decreased bone mineral density, and increased osteoblast activity. Introducing high doses of estradiol into this TMJ-DD model to mimic high-physiological levels resulted in enhanced degeneration of the articular fibrocartilage but reduced UAC-induced bone resorption [73].

Chemically-induced TMJ-DD typically constitutes either injection of complete Freund's adjuvant (CFA), formalin, or monosodium iodoacetate (MIA). In formalin-induced TMJ-

DD, cytokine expression in male and female rats was decreased by gonadectomy and increased by hormone administration [74]. Interleukin (IL)-6 expression increased in females during diestrus, proestrus, and estradiol or progesterone administration in ovariectomized female rats. Tumor necrosis factor alpha (TNF-α), IL-1β, and cytokineinduced neutrophil chemoattractant (CINC-1) expression increased with testosterone treatment after orchiectomy. In a MIA-induced model in rats, E2 enhanced the OA response in a dose-dependent manner by increasing pro-apoptotic genes and histologic characterization of fibrocartilage degradation and bone erosion [75]. In this study, a supraphysiological dose of 80 μg of estrogen replacement potentiated MIA-induced TMJ-DJD compared to the ovariectomy with placebo control group. When CFA and MIA were combined for a model of TMJ-DD in male and female rats, the female rats showed aggravated OA features compared to the males [76]. Further, female fibroblast-like synoviocytes (FLS) isolated from the TMJ synovial membrane were more sensitive to TNF-α treatment compared to males. Estrogen's effect in this process was confirmed by ovariectomy and estrogen receptor agonists. However, the studies were performed in young growing mice and it is established that estrogen inhibits TMJ growth in the young [77]. Therefore, the effects of estrogen in potentiating TMJ-DD in the young may result from inhibiting TMJ growth as opposed to modifying the progression of TMJ-DD.

Biphasic role of estrogen levels in mediating the sex dimorphism of TMD

At this time, we have no definitive answers to how estrogen signaling promotes TMD in females. However, there are four theories to explain the observed effects. First, fluctuations in estrogen levels promote TMD pain. Similar to TMD, the prevalence of migraines without aura is greater in females than in males but not at all ages. Before puberty, the prevalence of migraines is similar between the sexes. However, after puberty, migraines are 2–4 times more likely to occur in females than age-matched males with the peak prevalence occurring in women between the ages of 35–45. The estrogen withdrawal hypothesis posits that fluctuating estrogen levels pre and post-menstrual cycles and during peri-menopause predisposes women to migraines [78, 79]. Therefore, a similar mechanism may occur in TMD, whereby TMJ pathology maybe similar in the sexes but fluctuating levels of estrogen make women more likely to experience longer lasting pain. Second, estrogen protects the TMJ from degeneration and conversely low levels of estrogen predisposes post-menopausal women to TMJ-DD. The vast majority of studies have shown that women over the age of 50 are more likely than age-matched men to suffer from TMJ-DD [80–82]. One way that estrogen may protect the joint is by regulating the expression of protease inhibitors, such as A2M. Estradiol treatment increased A2m gene expression and mandibular condylar fibrocartilage immunostaining in wild-type (WT), skeletally mature mice. Interestingly, this same effect was not seen in ERα knockout mice [57]. Also, A2m and protease inhibitor 15 (Pi15) dosing studies in an organ culture model resulted in decreases in matrix proteases including MMP-9. However, other studies in bone have shown A2m upregulation via estradiol independent of either ERα or ERβ suggesting this is not the sole mechanism [83]. A2m has been shown previously to be a potential inhibitor of posttraumatic osteoarthritis in the knee [84] highlighting the potential for similar treatment to reduce TMJ degeneration utilizing A2m. Third, sex differences in estrogen signaling are contributing to TMD symptoms. ERβ signaling inhibits TMJ growth in female but not in male mice [71]. Also, a

negative hypothalamus ERα signaling pathway in female but not male mice has been discussed. Conditional deletion of ERα in hypothalamus Kiss1-expressing cells caused a two–fivefold increase in bone density, solely in females [85]. RNA sequencing data from the bone marrow from these mice revealed that many of the same genes were upregulated (A2M, Pi15, Col8a1) compared to ovariectomized, wild-type mice treated with estradiol in the mandibular condylar fibrocartilage, suggesting the potential for a hypothalamus Erα-negative signaling pathway in the TMJ in female but not in male mice. Taken together, ERβ and/or a hypothalamus ERα negative signaling pathway may cause inhibition of TMJ repair making women more prone to TMD. Lastly, differences in TMJ anatomy and structure may result in altered biomechanics that predispose the female joint to more mechanical fatigue. The male condyle is larger than the female, on average, and exhibits a longer condylar lingual length with long elliptical condyles compared to the smaller, round condyles of a female TMJ [86]. These anatomical differences result in sex differences in joint loading. Static and dynamic mechanical analyses of aged male and female articular fibrocartilage-subchondral bone units resulted in significant differences in energy dissipation and load to the tissues. In males, the subchondral bone with stands the majority of load whereas in females, the articular fibrocartilage bears a significant proportion of the load [87]. Dynamic stereometry assessment using Magnetic resonance (MR) and cone-beam computed tomography (CBCT) data were used to illustrate an increased energy density in the TMJ of female subjects suggesting an increase in biomechanical fatigue compared to males [88].

Periodontal disease and estrogen

Periodontal disease is a condition of infectious, inflammatory or combined origin that affects tissues surrounding and supporting teeth [89]. Both non-modifiable and modifiable factors are involved in its occurrence. Gingivitis and periodontitis are collectively known as periodontal diseases. The first one referrers to reversible gingival inflammation, while the other one describes a condition when the loss of alveolar bone and connective tissue accompanies gingival inflammation [90]. The role of estrogen in mediating periodontal diseases is biphasic with high levels promoting gingivitis, and low levels potentiating alveolar bone loss.

Estrogen and gingivitis

Two recent meta-analyses have concluded that conditions which raise estrogen levels (i.e., pregnancy and oral contraceptive use) are associated with an increase in the prevalence of gingivitis [91, 92]. However, the mechanism remains unclear. One way in which estrogen may potentiate gingivitis is by changing the composition of the oral microbiome. A traditional view of periodontal research focuses upon identification of select periodontopathic bacteria such as the “red complex” (*Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*) [93]. However, development of molecular-based approaches has allowed us to consider new models of pathogenesis in which periodontal disease is initiated by broadly-based dysbiotic and synergistic microbiota [94], including both cultivated and uncultivated microbes. Older studies found no definitive associations between elevated states of ovarian hormones and preferential enrichment of the subgingival microbiome for selected species [95, 96]. However, recent studies using next-generation

sequencing have found that despite stability of oral microbiome diversity, there was enrichment of certain bacteria taxa in African American [97] and Chinese pregnant women [98].

It now appears that pregnancy modulates the mother's immune system, but it does not necessarily suppress it. This may result in pregnant women responding differently to different types of microorganisms, which is also regulated by the different stages of pregnancy [99]. Estrogen-mediated effects are apparent in all major innate and adaptive immune cells, including neutrophils, macrophages, T cells and B cells [100]. However, estrogen by itself does not seem to affect gingival crevicular fluid cytokines levels. For example, it was shown that rising estrogen levels during pregnancy did not affect IL-beta or TNF alpha levels [101]. Furthermore in another study they found that there was no difference in IL-1 alpha, IL-1 beta, IL-8, TNFalpha, and SLPI mRNA levels in the GCF between samples from the 12th week of pregnancy and 4–6 weeks post-partum [102].

Estrogen deficiency and periodontitis

Menopause is associated with increased alveolar bone loss without changes in probing depths or in clinical attachment loss [103]. In addition menopausal women are more prone to osteoporosis, which has been associated with increased alveolar bone loss [104]. Finally, alveolar bone loss was found to be less severe in post-menopausal women with a history of HRT use [105]. Recent research has delineated the distinct roles of aging and estrogen deficiency on skeletal bone mass. New evidence illustrates that estrogen deficiency independently promotes the survival and increased activity of osteoclasts, resulting in increased bone resorption [106]. On the other hand, aging independently causes a decrease in osteoblasteogenesis [106] and an increase in cellular senescence [107]. Most cross-sectional studies have found a radiographic relationship between alveolar bone loss and osteoporosis [104], although it is unclear what the exact contributions of estrogen deficiency and aging are on alveolar bone loss.

Periodontitis is triggered by pathogenic microbes or microbial dysbiosis in a susceptible host, which results in the host inflammatory response causing soft tissue destruction and bone loss [108].

The complex host immune response involves cells of both the innate and adaptive immune response (Fig. 2). Bacteria and their products including lipopolysaccharides (LPS) trigger the initial production of cytokines such as TNFα, IL-1, IL-6, macrophage inflammatory protein-1 (MIP-1/CCL3) and macrophage chemoattractant protein (MCP-1) from neutrophils, monocyte/macrophages, fibroblasts and dendritic cells. Macrophages also secrete proteases such as matrix metalloproteinases (MMPs) that degrade extracellular matrix directly. TNFα and IL-1β stimulate the adaptive immune response with T cells and B cells, which have been shown to play a critical role in alveolar bone loss in periodontitis primarily through expression of receptor activator of NFκb ligand (RANKL) [109, 110]. RANKL binds to the RANK receptor on osteoclast precursors, inducing osteoclast differentiation and activation to resorb bone. Osteoblasts also produce osteoprotegerin (OPG), a member of the family of TNF receptors, which functions as a decoy receptor for RANKL. Binding of OPG to RANKL inhibits osteoclast differentiation and bone resorption

by mature osteoclasts. The OPG/RANK/RANKL system is the dominant, final mediator of osteoclastogenesis, and bone resorption is determined by the relative amounts of RANKL and OPG produced [111]. Gingival tissue from patients with periodontal infection, expresses higher levels of RANKL and lower levels of OPG [112]. In another study, confocal microscopy revealed that 50% of T cells and 90% of B cells expressed RANKL in diseased gingival tissue, whereas less than 20% of B cells and T cells expressed RANKL in healthy gingival tissue [113]. RANKL expression is highest in activated B cells, followed by T cells and monocytes [113]. Taken together these studies suggest that activated T and B cells play an important role in alveolar bone loss through enhanced RANKL production. Estrogen downregulates the production of cytokines by T cells (TNFα, RANKL), monocytes (IL-1, TNFα), and bone marrow stromal cells (IL-6, RANKL, GM-CSF, and M-CSF) and increases production of TGFβ by osteoblasts, resulting in decreased osteoclast number and activity [114–116]. Estrogen deficiency after menopause enhances the production of TNFα and RANKL by T cells [116], increases production of osteoclast precursors [116, 117] and has both a pro-apoptotic effect on osteoblasts and an anti-apoptotic effect on osteoclasts (Fig. 2). Therefore, it is likely that periodontal disease and alveolar bone loss would both accelerate after the menopausal transition, and be prevented by estrogen replacement. The Osteoperio study determined that history of HRT in postmenopausal women was associated with lower alveolar crestal height (ACH), suggestive of less alveolar bone loss, although, serum estradiol (E2) levels did not correlate with ACH [105]. Based on the National Health and Nutrition Examination Survey (NHANES III) database, there was also an association between HRT use and decreased clinical attachment loss [118]. However, a recent meta-analysis concluded that HRT in post-menopausal women did affect radiographic bone loss or clinical attachment loss [119]. A possible reason for these discordant results, comes from a recent paper that analyzed the NHANES database and found that HRT and clinical periodontal measures were strongest among women with high vitamin D levels [120].

Conclusions

Estrogen signaling plays a significant role in the sex dimorphism of periodontal diseases and temporomandibular joint disorders. Estrogen signaling is complex and the varying levels of estrogen during a woman’s lifetime may play a unique role on oral diseases. For example, fluctuating levels of estrogen during childbearing ages and peri-menopause may predispose women to facial pain, increased estrogen levels during pregnancy may cause changes in the oral microbiome leading to gingivitis and low levels of estrogen post-menopause may potentiate temporomandibular joint degeneration and alveolar bone loss. Furthermore, there is sex-specific estrogen receptor signaling, that also contributes to the sex dimorphism of oral disease.

Currently, HRT appears to have only modest impact on the progression of temporomandibular joint disease and periodontal clinical attachment loss. However, different estrogen signaling pathways may be involved in promoting anabolic actions in mandibular condylar fibrocartilage or mediating facial pain, and may differ between specific TMJ diseases. Additional developments in selective estrogen receptor modulators may hold further promise for future pharmaceutical therapies. For example, ERα agonist therapy may prevent TMJ degeneration progression in post-menopausal women but may have little effect

on post-menopausal women suffering from temporomandibular myalgia or TMJ disc disorders. Knowledge of sex and age-specific estrogen signaling effects is vital for the development of strategies for oral tissue remodeling and homeostasis.

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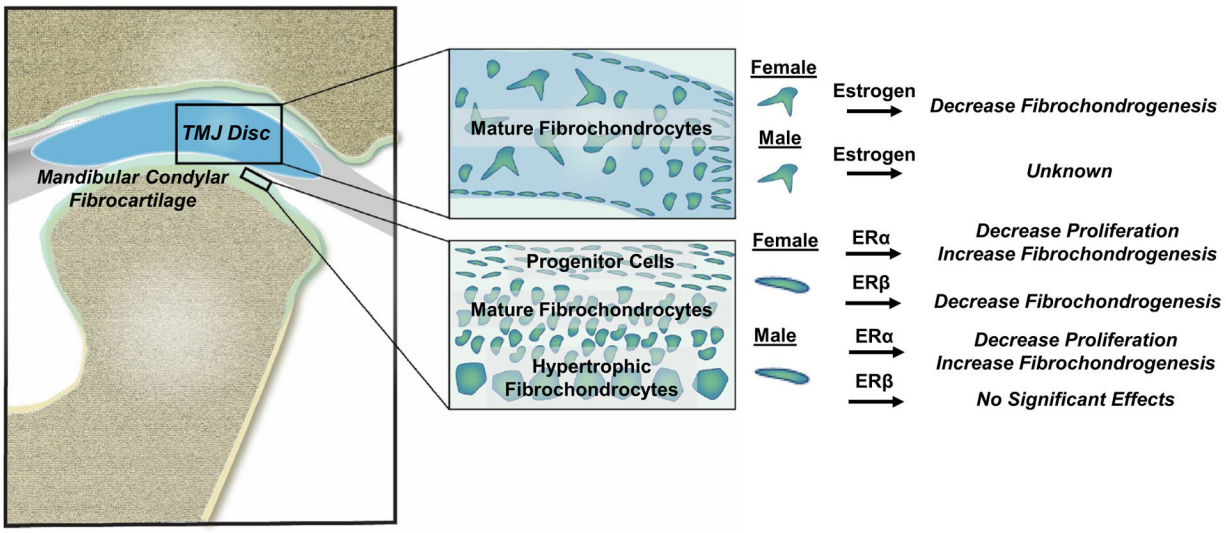

Fig. 1.

Role of estrogen signaling via estrogen receptors alpha (ERα) and beta (ERβ) on cells from the temporomandibular joint disc and condylar fibrocartilage

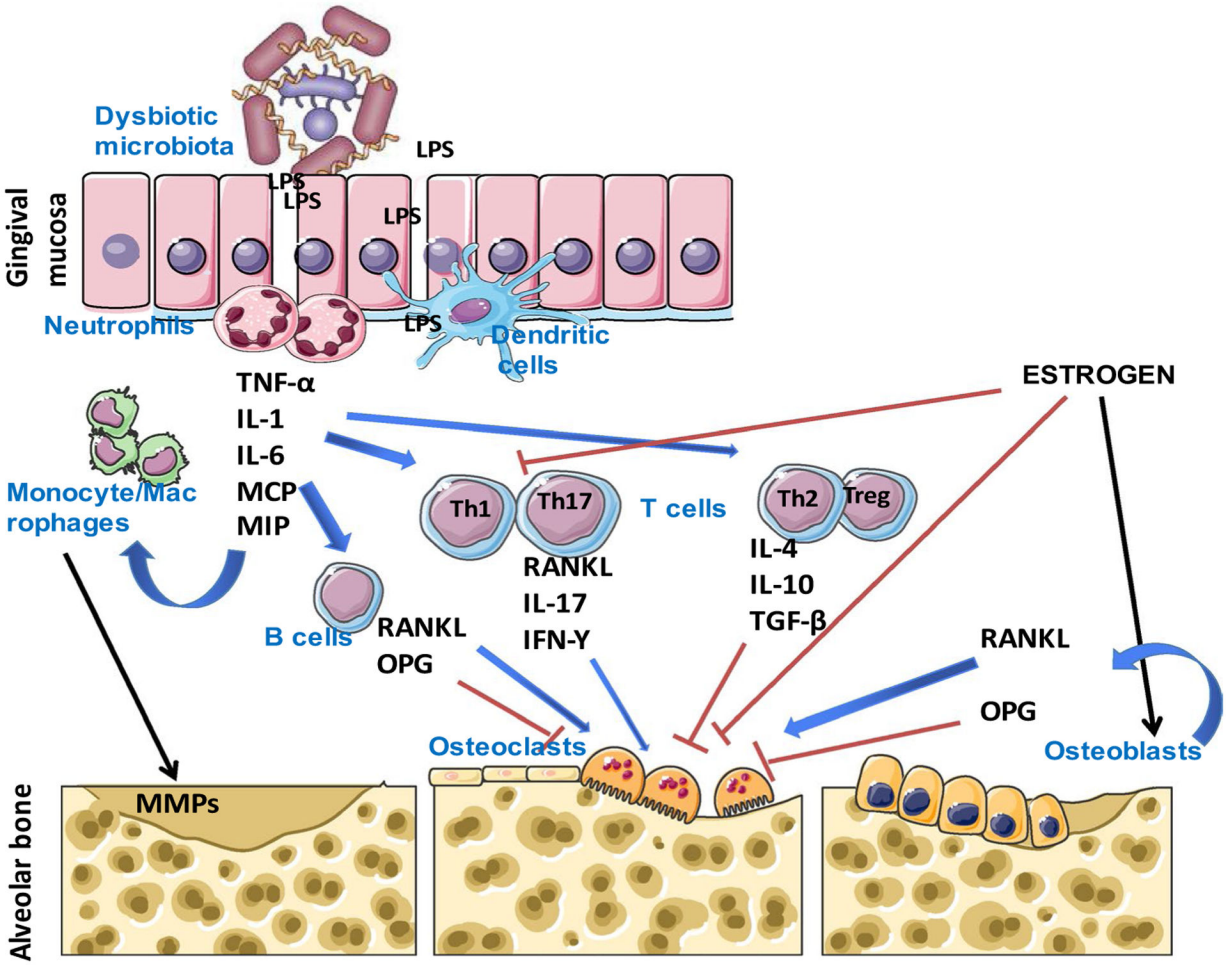

Fig. 2.

Working model of potential role of estrogen in mediating periodontal disease-induced alveolar bone loss

Table 1

Role of estrogen on the TMJ disc and condylar fibrocartilage

Sex	Animal model (age)	In vitro, in situ, in vivo	Hormone treatment (study duration)	Estrogen-induced response	Study
TMJ disc					
Female	Baboon (5 years old)	In vitro	10 nM 17β-estradiol (48 h)	Reduction in promoter activity and gene expression of proteoglycan 4	McDaniel et al. [49]
Female	New Zealand white rabbits (20 weeks old)	In vitro	20 ng/mL 17β-estradiol and/or 0 – 100 ng/mL relaxin (24 h)	Increased relaxin-induced activity of collagenase and stromelysin	Kapila and Xie [50]
Female	New Zealand white rabbits (22 weeks old)	In situ	20 ng/ml β-estradiol, 0.1 ng/mL relaxin, or both (48 h)	Increased collagenase-1 and stromelysin-1 expression	Naqvi et al. [51]
Female	New Zealand white rabbits (18 weeks old)	In vivo	20 ng/kg body weight 17β-estradiol and/or 5 mg/kg progesterone and/or 23.3 μg/kg relaxin (48 h)	Estradiol and relaxin both alone and synergistically increased GAG and collagen content	Hashem et al. [52]
Female	C57BL/6J mice, (12 weeks old)	In vitro	0.1–0.5 ng/mL 17β-estradiol (48 h)	Increased MMP-9 and MMP-13 levels	Ahmad et al. [68]
Female and Male	C57BL/6J mice (12 weeks old)	In vitro	None	TMJ disc cells have a higher expression of ER-α than ER-β. Female cells expressed higher concentrations of ERα and ERβ compared to male cells	Wang et al. [66]
TMJ disc—osteoarthritis models					
Female	Wister rat (45 days old)	In vivo	Females: 50 μg/kg 17β-estradiol and 8 mg/kg progesterone; (7 days)	Increased the release of IL-6 in female rats after formalin injection	Torres-Chavez et al. [74]
Female and Male	Sprague-Dawley rats (8 weeks old)	In vivo	5 mg/mL ICI 182,780 and 0.5 μg/mL tamoxifen (7 days)	Increased cartilage degradation and bone deterioration in female rats after Freund's complete adjuvant combined with monosodium iodoacetate treatment	Xue et al. [76]
TMJ condylar fibrocartilage					
Female	Sprague-Dawley rats, (8 weeks old)	In vitro	10 nM 17β-estradiol (12 days)	Decrease in fibrocartilage thickness and cell proliferation and increase in collagen type 10 (Col10) in hypertrophic chondrocyte zone	Talwar et al. [53]
Female	Wistar rats (4 weeks old)	In vivo	50 μg/100 g body weight 17β-estradiol (2 weeks)	Increase in fibrocartilage thickness and subchondral bone volume	Yasuoka et al. [55]
Female	C57BL/6J WT and ERβKO mice (21 days old)	In vivo	10 ng/g/day 17β-estradiol (28 days)	WT: decrease in cell proliferation, decrease in ERα expression and increase in sclerostin expression. ERβKO: increase in collagen type 2 (Col2) and sclerostin expression	Chen et al. [56]
Female	C57BL/6J WT and ERβKO mice (7, 49, 120 days old)	In vivo	None	49 and 120 days old: increase in fibrocartilage thickness, gene expression (Col10, Pthrp, and OPG) and subchondral bone volume, and decrease in gene expression (Rankl and Ihh) and number of osteoclasts in ERβKO compared to WT	Kamiyaetal. [71]
Female	C57BL/6J WT and ERαKO mice OVX (7 and 17 weeks old)	In vivo	7-week old: 7 ng/g 17β-estradiol/ body weight 17-week old: 11 ng/g 17β-estradiol/body weight (4 weeks)	7 weeks old: estrogen via ERα promotes fibrochondrogenesis by upregulating sclerostin and inhibiting canonical Wnt	Robinson et al. [57]

Sex	Animal model (age)	In vitro, in situ, in vivo	Hormone treatment (study duration)	Estrogen-induced response	Study
				signaling 17 weeks old: Estrogen via ERα reduced protease activity by upregulating protease inhibitors	
Female and male	C57BL/6J ERβKO mice (21 days old)	In vivo	None	Decreased occlusal loading (DOL) resulted in decreases in Col10 expression and bone volume. No differences in male or female response to DOL in ERβKO mice	Polur et al. [121]
Female and male	Sprague-Dawley rats, (2,4,8 weeks old and 4 and 12 months old)	In vivo	None	Estrogen receptor α and β expression was overall higher in males	Yu et al. [67]
Female and male	Wistar rats (3 months old)	In vivo	50 μg/day 17β-estradiol (21 days)	Decreased cartilage thickness and accelerated calcification into bone	Figueroba et al. [58]
Male	C57BL/6J WT and ERαKO mice (7 weeks and 9 months old)	In vivo	None	7 weeks old: ERαKO mice had increase in cell number and decrease in Sox9, Col10, Runx2, and DMP1 gene expression compared to WT 9 month old: ERαKO mice had increase in cell number and no significant difference in gene expression or osteoarthritic scoring compared to WT	Robinson et al. [69]
Male	C57BL/6J WT and ERβKO Mice (21 days old)	In vivo	10 ng/g/day 17β-estradiol (4 weeks)	Increased Col2 expression and trabecular thickness in both WT and ERβKO	Robinson et al. [72]
Unspecified	Rabbits unspecified species (neonate)	In vitro	1 μM-1 pM, 17 β-estradiol (72 h)	Increased cell proliferation and proteoglycan synthesis up through 10^{-8} M after which estradiol reduced proliferation and proteoglycan synthesis.	Cheng et al. [54]
TMJ condylar fibrocartilage—osteoarthritis models					
Female	Sprague-Dawley rats (age unspecified)	In vivo	0 μg/day, 20 μg/day, 80 μg/day 17β-estradiol (3 weeks)	Estrogen aggravated TMJOA through subchondral bone erosion in monosodium iodoacetate model	Wang et al. [75]
Female	Sprague–Dawley Rats (6 weeks old)	In vivo	0.2 mg/kg/day- 0.5 mg/kg/day, 17β-estradiol (8 weeks)	High doses of estradiol enhanced degeneration of the articular fibrocartilage and reduced UAC-induced bone resorption	Ye et al. [73]