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Estrogen signaling impacts temporomandibular joint and periodontal disease pathology

A Project Submitted to

The College of Dentistry, University of Baghdad, Department of Periodontics in Partial Fulfilment for the Bachelor of Dental Surgery

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بسم الله الرحمن الرحيم

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا ۖ إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

سورة البقرة (آية 32)

Certification of the Supervisor

I certify that this project entitled **" Estrogen signaling impacts temporomandibular joint and periodontal disease pathology"** was prepared by **(Ibrahim Haider Sadeq)** under my supervision at the College of Dentistry / University of Baghdad in partial fulfilment of the graduation requirements for the Bachelor degree in dentistry.

Signature
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Dedication

I dedicate this project to Almighty God, my creator, my strong pillar, my source of inspiration, wisdom, knowledge and understanding. He has been the source of my strength and on His wings only I have soared

And with all the love and respect, I dedicate this project to my lovely mother, father, brothers, and my friends for their great support and for always believing in me.

To all my friends and colleagues.

Finally, to my supervisor who encourages me to keep going.

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Thank everyone who helped me in the completion of the search for scientific truth

List of contents

List of tables

List of figures

List of abbreviation

Abbreviation	Scientific name
ILs	Interleukins
PGE2	Prostaglandin E2
TN-α	Tumor necrosis alpha
TLR	Toll-like receptor
MMP	Matrix metalloproteinase
CVD	Cardiovascular disease
HRT	Hormone replacement therapy
PLBW	Preterm low birth weight
TMJ	Temporomandibular disease
TMD	Temporomandibular disorder
DC-TMD	Diagnostic criteria for temporomandibular disorder
GnRH	Gonadotropin releasing hormone
FSH	Follicle stimulating hormone
LH	Luteinizing hormone
GCF	Gingival crevicular fluid
ERα	Estrogen receptor alpha
ERβ	Estrogen receptor beta
GPR30	G protein-coupled receptor 30
ERE	Estrogen response elements
NTD	N-terminus domain
ECM	Extracellular matrix
OPG	Osteoprotegerin
PCR	Progressive condylar resorption
Pi15	Protease inhibitor 15
A2M	Alpha-2-macroglobulin

GCF	**Gingival crevicular fluid**
SLPI	**Secretory Leukocyte Protease Inhibitor**
PG	**Pyogenic granuloma**
VEGF	**Vascular Endothelial Growth Factor**
bFGF	**b-Fibroblast Growth Factor**
LPS	**Lipopolysaccharides**
MIP-1	**Macrophage inflammatory protein-1**
MCP-1	**Macrophage chemoattractant protein-1**
RANKL	**Receptor activator of NFκb ligand**
TGFβ	**Transforming growth factor beta**
ACH	**Alveolar crestal height**
E2	**Estradiol**
NHANES	**National Health and Nutrition Examination Survey**

Abstract

Background: women experience a higher incidence of oral diseases including periodontal diseases and temporomandibular joint disease 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 temporomandibular joint 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, temporomandibular joint 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.

Aim of the study: to assess the impact of estrogen signaling on temporomandibular joint and periodontal disease pathology.

Conclusion: based on the available evidence from different researches, we conclude that: estrogen deficiency can trigger temporomandibular disorders by promoting the inflammation and bone resorption that result in disc inflammation, osteoarthritis, displacement, and condylar resorption in the temporomandibular joint. While the impact of estrogen deficiency on the periodontium induces gingivitis through its major effects on the innate and adaptive immune system and bone resorption that leads to periodontitis.

Keywords: Estrogen; Temporomandibular joint; Periodontal disease.

Aim of the study

To assess the impact of estrogen signaling on temporomandibular joint and periodontal disease pathology

Chapter one
Review of literature

1.1. Periodontal Disease:

1.1.1. Introduction:

Periodontal disease is a chronic inflammatory disease that affects the soft tissue and the bone surrounding teeth caused by an organized community of bacteria called dental plaque. Bacteria trigger an immune-inflammatory response that ultimately leads to an irreversible loss of bone supporting the tooth and leads to tooth loss [(1)].

The milder form of periodontal disease, gingivitis, represents inflammation contained within the gingival epithelium and the underlying connective tissue, which commonly precedes the onset of periodontitis. Although gingivitis is reversible, it often persists as chronic inflammation despite daily self-performed control of the dental plaque biofilm and periodic professional care and therefore represents a constant risk for periodontitis, which is irreversible in susceptible individuals [(2)].

The main culprit identified in periodontitis is the bacterial biofilm growing on the tooth surfaces [(3)]. While the host response determines the progression of the disease along with factors like local factors e.g. calculus, genetics, environmental factors, systemic health of the patient, lifestyle habits and various social determinants also play a role [(4)].

1.1.2. Etiology of periodontal diseases:

The primary causative factor of periodontal disease is the bacterial biofilm which is called dental plaque. Dental plaque is a community of microorganisms found on the surface of teeth or other hard surfaces like dentures and embedded in a matrix of polymers of both host and bacterial origin [(5)].

A number of local factors in the gingival environment act as site-specific problems which predispose towards the accumulation of plaque deposits and prevent their removal. These are called plaque-retentive factors [6]. Calculus (often referred to as 'tartar') is plaque, which has become calcified and hardened. Calculus is a plaque-retentive feature and renders effective oral hygiene more difficult. Calculus can form above the gum line (supragingival) and below the gum margin (subgingival). As periodontal disease progresses, the shallow space between the gum margin and the tooth (the sulcus or gingival crevice) deepens to form a periodontal pocket in which the biofilm and subgingival calculus accumulate and which is more difficult to keep clean [7].

Other local plaque retentive factors are tooth anatomic factors and iatrogenic factors. Tooth anatomic factors include cervical enamel projection, enamel pearl, developmental grooves such as palate-gingival groove, root proximity and open contacts. Iatrogenic factors are tooth restorations having marginal discrepancies, overhanging restorations and subgingival margin placement. Others include root fracture, cervical root resorption and cemental tears [8].

1.1.3. Pathogenesis of periodontal diseases:

Periodontitis is a chronic inflammation that develops due to a destructive tissue response to prolonged inflammation and a disturbed homeostasis (dysbiosis) in the interplay between the microorganisms of the dental biofilm and the host. An imbalance of micro-organisms forming the dental plaque (dysbiosis) is a major triggering factor for chronic gingivitis and periodontitis [9]. In addition, periodontitis is associated with, and probably caused by, an altered dynamic interaction among specific subgingival microbes, host immune responses, hazardous environmental exposure and genetic factors [10]. To date, almost 800 different species of bacteria have been identified and characterized in human

dental plaque. Of relevance, the putative pathogens include Gram-negative and -positive members, such as *Treponema denticola, Agregatibacter actinomycetemcomitans,* and *Porphyromonas gingivalis* [(11)]. Mechanistically, infections usually lead to gingival lesions with contamination of tissues surrounding the teeth. Then, the lesion progresses to periodontitis once bacterial infection, and the subsequent inflammatory response, tackles the root surface, penetrating the supporting structures of the teeth [(9)].

In general, the inflammation process begins with phagocytes (neutrophils and macrophages) that migrate to the lesion site. Importantly, this process is, at least in part, promoted by the gingival epithelium that releases chemical mediators including interleukins (ILs), prostaglandin E2 (PGE2), tumor necrosis factor alpha (TNF-α), that recruit neutrophils [(12)]. Furthermore, these phagocytic cells express on their plasma membrane specific receptors that recognize and bind surface molecules of bacteria (i.e., Toll-like receptors, TLRs) [(12)]. Analogously, the plasma proteins of the complement system react with one another to make pathogens more susceptible to the action of these phagocytic cells [(12)]. The function of this initial response includes the killing and elimination of microbes followed by an efficient clearance of the resulting cellular debris (necrotic tissue and apoptotic neutrophils) by mononuclear cells, such as monocytes and macrophages. It is worth stressing that in an effective and healthy immune system, there is no damage to the tissue surrounding the tooth and the bacterial insult is efficiently removed [(13)]. However, when microbial species continue to grow, or if there is a defective/altered immune response, the acute periodontal inflammation becomes chronic and additional mediators are produced [(14)]. These events result in the recruitment of more immuno-cell types, such as T-cells and monocytes. Then, this prolonged inflammatory process induces alveolar bone resorption, by osteoclasts, and degradation of ligament fibers by (MMPs), as well as the formation of the granulation tissue. Moreover, as discussed above, this

sustained chronic inflammatory process can lead to noxious effects that could link periodontal disease to other disorders including diabetes [15]. This sustained chronic inflammatory process can lead to noxious effects that could link periodontal disease to other disorders including diabetes and cardiovascular diseases (CVD), as seen in (Figure:1-1):

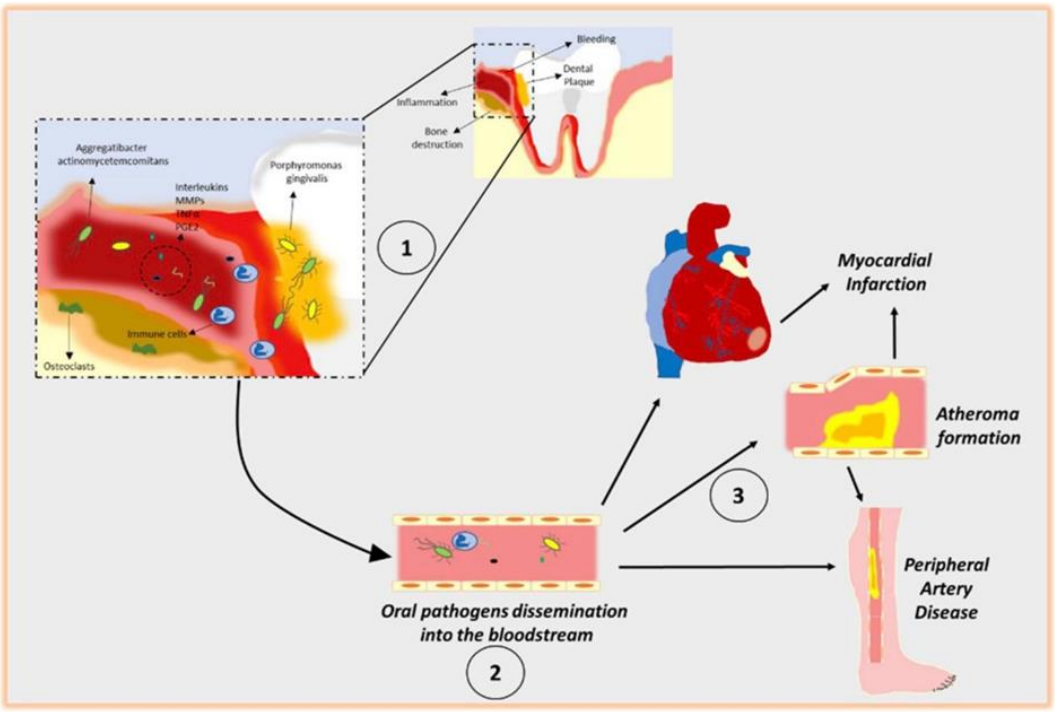

Figure:(1-1): Schematic representation of inflammatory mechanisms linking periodontitis to CVDs. (1) The imbalance in pathogens of the biofilm leads to gingival epithelium inflammation that releases chemical mediators, such as interleukins (ILs), prostaglandin E2 (PGE2), tumor necrosis factor alpha (TNF-α) and MMPs, that recruit immune cells. This inflammatory response induces alveolar bone reabsorption, by osteoclasts. (2) At a chronic stage, oral pathogenic dissemination into the bloodstream leads to the onset of CVDs including atherosclerosis, myocardial infarction and peripheral artery disease (3).

1.1.4. Risk Factors of periodontal diseases:

The risk factors for periodontal diseases can be broadly classified as individual and local as shown in (Table:1-1), which provides a simple classification system for these factors [16].

Table:1-1: Classification system for periodontal risk factors

Individual Risk Factors		Local Risk Factors
Modifiable Risk Factors	Nonmodifiable Risk Factors	
Smoking	Age	Root proximity
Diabetes	Genetics	Tooth malposition
Obesity	Gender	Enamel pearls and cementoenamel projections
Others such as stress, osteoporosis, alcohol, nutritional deficiencies	Ethnicity	Root abnormalities such as palatoradicular grooves, cemental tears
		Others such as subgingival restorations, open contacts

Hormonal fluctuations in the female patient may alter the status of periodontal health. Such changes may occur during puberty, the menstrual cycle, pregnancy, or menopause [17]. Changes may also be associated with the use of oral contraceptives. The most pronounced periodontal changes occur during pregnancy, as a significant proportion of pregnant women suffer from pregnancy gingivitis. Women on hormonal replacement therapy (HRT) and oral contraceptives experience increased gingival inflammation [18], while with oral contraceptives, this increase in gingival inflammation is mainly related to the duration of use as it has been suggested that prolonged use of oral contraceptives may detrimentally affect the periodontium.

Offenbacher *et al.* **(S. Offenbacher et al., 1996)** [19] found significantly more periodontal attachment loss among mothers of preterm low birth weight

(PLBW) infants compared with mothers of normal-term infants. Similarly, several other studies have suggested an adverse influence of periodontal disease on the course of pregnancy. It has been suggested that periodontal disease may increase the risk of having (PLBW) infants. This outcome is thought to be the effect of biologic mediators of inflammatory processes such as (PGE2) and (TNF). The common bacterial product lipopolysaccharide also may have a triggering role in adverse change of the course of pregnancy [20].

1.2. Temporomandibular joint:

1.2.1. Introduction:

The temporomandibular joint (TMJ) is ginglymoarthrodial joint located on each side of the cranium. It is located anterior to the external acoustic meatus and posterosuperior to the masseter muscle. It is located between the mandible's condyle and the mandibular fossa and articular eminence of the temporal bone [21].

Temporomandibular joint has some common features with the other joints in the human body. (TMJ) includes an articular disc that could be seen in some other joints in the human body. (TMJ) has bony articular surfaces, articular capsule, synovial membrane, and ligaments just like other joints, but (TMJ) has differences that make it special among other joints in the body. (TMJ) of each side is connected with a single mandible that necessitates the harmonic and coordinated function of each (TMJ). Articular surfaces of (TMJ) are covered by fibrocartilage, while many other joints have hyaline cartilage. (TMJ) is the only joint in the human body to have a rigid endpoint of closure with the dental arches on each jaw contacting each other that is called occlusion. (TMJ) is the last joint to begin its development in the 7th to 10th intrauterine week [22].

1.2.2. Anatomy:

Temporomandibular joint is composed of a synovial cavity, articular cartilage and a capsule that covers the same joint. We find the synovial fluid and several ligaments. The joint is the union of the temporal bone cavity with the mandibular condyle [23].

a. **The cranial surface of temporomandibular joint (TMJ) consists of the squamous area of the temporal bone;** it takes the name of glenoid fossa and welcomes the condyle of the jaw. The anterior limit of the glenoid fossa of the temporal bone constitutes the articular eminence, which forms a medial bone prominence at the posterior border of the zygomatic bone. On the lateral surface of the articular eminence, there is a bone ridge, known as the articular tubercle, near the root of the zygomatic process [23].

b. **The articular disc** that covers the condyle and interposes below the glenoid fossa has a biconcave or oval shape; the cartilaginous disc has an anterior (about 2 mm) and posterior (about 3 mm) portion, with a thinner diameter in the middle. The anterior portion of the articular disk is in contact with: the joint capsule; articular eminence; condyle; the upper area of the lateral pterygoid muscle. The posterior portion of the articular disk relates to: bilateral retro-disc tissue (behind the condyle), glenoid fossa; condyle; temporal bone. The medial and lateral aspect of the cartilaginous disc is attached to the condylar formation of the mandible. The edges of the disc partly fuse with the fibrous capsule surrounding the joint [24].

c. **Several ligaments** manage the Temporomandibular joint forces and send multiple proprioceptive afferents [25] as seen in (Figure:1-2):

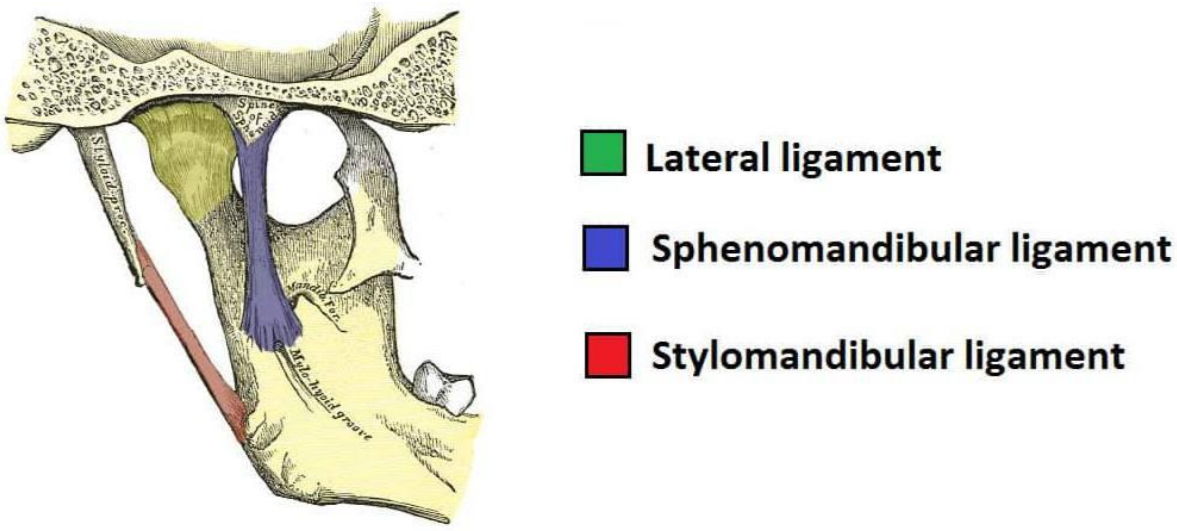

Figure:(1-2): Temporomandibular joint ligaments

1.2.3. Function of Temporomandibular joint:

When the mouth opens there is a combination of rotational movement of the discomandibular space and action of the translational discotemporal space; the rotation occurs before the translation. The condyle can move laterally through a rotation and then an anterior sliding of the same condylar structure, and an anterior translation/rotation in the medial direction of the opposite condyle. The condyle can move backward, while the opposite condyle slides forward. The bilateral or ipsilateral TMJ protrusion occurs by anterior sliding [(26)].

The complex movements of TMJ allow multiple functions [(26)]:

1) Chewing
2) Sucking
3) Swallowing
4) Phonation
5) Facial expressions
6) Breathing
7) Protrusion, retrusion, lateralization of the jaw

8) Opening the mouth
9) Maintain the correct pressure of the middle ear

1.2.4. Temporomandibular disorders:

Temporomandibular disorders (TMDs) are one of the most prevalent orofacial pain disorders, and may be arthrogenous and/or myogenous in origin. It is estimated that 5% to 12% of the population may be affected by these disorders. The etio-pathogenesis of (TMD) has shifted from early gnathologic concepts to the current biopsychosocial model [(27)]. (TMDs) and occlusion thus became one of the most controversia topics in dentistry. Evidence-based dentistry today has challenged some of the previously held views, by closely scrutinizing the studies and clinical reports from the past. However, it is well documented that certain (TMDs) can lead to occlusal changes. Thus, many occlusal changes, especially those that manifest with acute changes in occlusion, may be sequela to (TMDs) rather than the causation of (TMDs) [(28)].

These changes may be subsequent to developmental, degenerative, systemic, adaptive, benign, and malignant disorders. These patients may often present to the dental practitioner with subjective, and sometimes objective, signs and symptoms of a change in occlusion. Determination of the underlying temporomandibular disorder (TMD) responsible for the occlusal changes is crucial for treatment planning and successful management [(29)].

Changes in occlusion may occur secondary to temporomandibular disorders of the temporomandibular joint or the associated musculature myotonic muscular dystrophy (MMD). The Diagnostic Criteria for Temporomandibular Disorders (DC-TMD) is the most commonly accepted classification for (TMDs), it subclassifies (TMD) into joint pain, joint disorders, joint diseases, fractures, and congenital or developmental disorders. (MMDs) include muscle pain,

contracture, hypertrophy, neoplasm, movement disorders, and masticatory muscle pain attributed to central or systemic pain disorders [30].

Changes in occlusion secondary to temporomandibular disorders may be acute (when it develops suddenly) or chronic (when occlusal changes are gradual over a period of months to years). The changes in occlusion include posterior open bite, anterior open bite, facial asymmetries, midline deviations, crossbites, and miscellaneous (such as loss of vertical dimension, and heavier occlusal contacts) [31]. These changes may occur as a consequence of TMJ-related pathologies or muscle-related conditions, and may manifest as acute or chronic changes in occlusion. Changes in occlusion may follow increased intraarticular pressure, loss of bone support or (MMD) resulting from muscle fatigue, electrolyte imbalance, or deep pain inputs. Muscle contraction may also cause positional changes in the jaw, which may vary depending on the muscle involved [32].

A list of temporomandibular disorders and the changes in occlusion secondary to TMDs are shown in (Table:1-2):

Table:1-2: Changes in occlusion secondary to TMDs

Condition	Anterior occlusion	Posterior occlusion	Midline shift	Onset
Spasm of masseter, medial pterygoid, and/or temporalis muscle	Unaffected	Ipsilaterally feels heavy. Not usually measurable to patient	Unaffected	Rapid

TMJ condylar hypoplasia: Degenerative joint disease, Arthritis, Idiopathic condylar resorption	Mild: Unaffected	Mild: Hyper occlusion on ipsilateral distalmost tooth	Mild: Unaffected	Gradual
	Advanced: Open	Advanced: Occlusion only on distalmost tooth	Advanced: Toward the side of condition	
Lateral pterygoid shortening, spasm, contracture	Hyper-occlusion	Ipsilateral hypo-occlusion or no occlusion	Away from side of condition	Rapid
Disc displacement	Unaffected	Ipsilateral hyper-occlusion	unaffected	Rapid
TMJ inflammation	Unaffected	Ipsilateral hypo-occlusion or no occlusion	Unaffected	Rapid
Dislocation	May occlude on some teeth	May occlude on some teeth	Markedly away from the side of condition	Rapid

1.3. Female hormones:

1.3.1. Introduction:

Hormones are specialized regulatory molecules that influence reproduction, development and growth, internal environment maintenance, and energy production, consumption, and storage. Physiological/pathological signs of hormonal changes can be seen in practically all types of tissue cells. Hormones play important roles in the growth and maintenance of periodontal tissues. Deficiency of such hormones, especially the steroidal hormones, leads to periodontal diseases [(33)]. Sex hormones have also been identified to affect the pathogenesis of periodontal diseases, as hormonal changes in the oral cavity influence the physiology of host–parasite interactions [(34)].

Female hormonal system include: Gonadotropin releasing hormone (GnRH), Follicle stimulating hormone (FSH) and luteinizing hormone (LH) and Estrogen and progesterone [(35)].

Stages of a woman's life can be divided into the followings [(36)]:

I. Puberty
II. Menstrual cycle
III. Pregnancy
IV. Menopause

1.3.2. Estrogen:

1.3.2.1. Introduction:

Sex steroid hormones can directly and indirectly affect cell proliferation, differentiation, and development in target tissues. Among these, estrogens are an important class of female sex hormones that are involved in the development of secondary sex characteristics in women. Estrone, estradiol and estriol are the

main three naturally occurring estrogens. Among them, estriol, which exhibits the least activity, is the most abundant [37].

Estradiol is the most potent estrogen and is produced by the testis, ovary, placenta, and other distant organs. The ovary secretes estrone, which is the primary source in both women and males. In peripheral tissues, they are converted to androstenedione by extragonadal conversion. Estriol is formed when estradiol and estrone are combined, and it is the most easily identifiable form in the urine [38].

Estrogens have been traditionally reported to have physiological functions involved in the development of breast tissue and sexual organs, regulations of the menstrual cycle and reproduction, and maintenance of our bone density. However, recent reports suggest its cognitive and neuroprotective effects and anti-inflammatory roles [39].

Estrogens exert their effects via estrogen receptors. There currently are three known classes of receptors, estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and G protein-coupled receptor 30 (GPR30). ERα and ERβ are composed of various functional domains and have several structural regions in common, the amino- terminal domain (also known as N-terminus domain NTD) and estrogen response elements (ERE) [40]. Since estrogens are steroid hormones, they can exert their direct effects by entering the plasma membrane and taking estrogen receptor complexes to the cell nucleus and interacting and binding directly onto the (ERE) of intracellular (ERα) and (Erβ). Otherwise, they can indirectly exert their effects by activating intracellular signaling cascades via interacting with estrogen receptors [41].

1.3.2.2. The role of estrogen on temporomandibular joint structures:

A. Effects of estrogen on temporomandibular joint disc:

The temporomandibular joint disc is made up of a complex extracellular matrix (ECM) composed of collagen fibers, proteoglycans, and glycoproteins. The ECM provides structural support to the TMJ disc, and it is essential for the proper functioning of the joint. Estrogen signaling is crucial for the synthesis and organization of (ECM) components. It regulates the production of collagen and proteoglycans, ensuring that the (ECM) is maintained in optimal condition. Estrogen signaling also influences the degradation and turnover of (ECM) components, ensuring that damaged (ECM) components are repaired or replaced [(42)]. Estrogen signaling also plays a critical role in regulating the inflammatory response in the (TMJ) disc. Inflammation is a natural response to injury or infection, but chronic inflammation can lead to tissue damage and pain. Estrogen signaling helps to modulate the inflammatory response in the (TMJ) disc, reducing the risk of tissue damage and pain. Estrogen deficiency is associated with an increased risk of (TMJ) disorders, including osteoarthritis and disc displacement [(43)].

Osteoarthritis is a degenerative joint disease that affects the temporomandibular joint. It is characterized by the breakdown of cartilage in the joint. Estrogen deficiency accelerates this process by reducing the production of collagen and proteoglycans in the (TMJ) disc. This leads to a decrease in the structural integrity of the joint, increasing the risk of osteoarthritis [(44)].

Disc displacement is another temporomandibular disorder associated with estrogen deficiency. It occurs when the (TMJ) disc is displaced from its normal position, leading to pain and dysfunction. Estrogen deficiency weakens the collagen fibers in the (TMJ) disc and increasing the risk of disc displacement [(45)].

B. Effects of estrogen on the mandibular condylar fibrocartilage:

One of the factors associated with the onset of temporomandibular joint disorders, in particular, condylar bone lysis, is the decline in estrogens because the 17β-estradiol form has various functions that protect joints [(46)].

First, it has a releasing effect on osteoprotegerin (OPG), a protector of inflammatory mechanisms. Therefore, women with a lack of this circulating hormone have increased inflammatory cytokines, inhibiting the formation of new bone, consequently promoting condylar resorption as well as a decrease in bone density. Estrogen is an important modulator or bone metabolism. It has an effect on osteoblast differentiation, reducing cell proliferation and differentially regulating the expression of the extracellular matrix, which also explains molecular mechanisms of bone growth and remodeling by estrogens. Estrogen increases inflammation and decreases bone resorption [(47)].

Secondly, 17β-estradiol plays a role in matrix metalloproteinase (MMPs) signaling. (MMPs) are responsible for bone and cartilage destruction and are produced by osteoclast, and 17β-estradiol is involved in osteoclast differentiation and activation, as well as in metalloproteinase transcription [(48)].

Progressive condylar resorption (PCR) is a condition in which low levels of estrogens have been found and which has a higher prevalence in women. According to Gunson **(Gunson MJ, 2012)** [(49)], it is influenced by the presence of three group of factors: occlusion, local and systemic factors. The purpose of the study was to evaluate the influence of sex hormones on condylar resorption, and 96% of the women with (PCR) evaluated were found to have low levels of 17β-estradiol or a history of extremely irregular menstrual cycles, 62% of them met both criteria. 17β-estradiol deficiency is described as a systemic factor for (PCR) [(49)]. Other studies also support the idea that sex hormones, especially estrogens, play a role in bone, cartilage and disc tissue regulation. To reinforce the above,

an (MMP) elevation has been found in patients with severe (PCR), which would initiate the degradation process for the mandibular condyle's extracellular matrix [50].

1.3.2.2. Estrogen signaling via nuclear estrogen receptors in temporomandibular joint:

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. 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. Further, (ERs), either dependently or independently of ligand binding, interact with other transcriptional pathways through protein–protein interactions like involving phosphorylation modifications [51].

Overall, there are limited data detailing the role of estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) in the (TMJ). The effect of estrogen via Erα on mandibular condylar fibrocartilage morphology, matrix production, and protease activity was assessed in 7 and 17-weeks 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) [52]. In male mice, estradiol via ERα mediates mandibular condylar fibrocartilage growth and maturation in young male mice using global (ErαKO) models. 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 [53]. A summary of the general effects of estrogen on the disc and condylar fibrocartilage can be seen in (Figure:1-3).

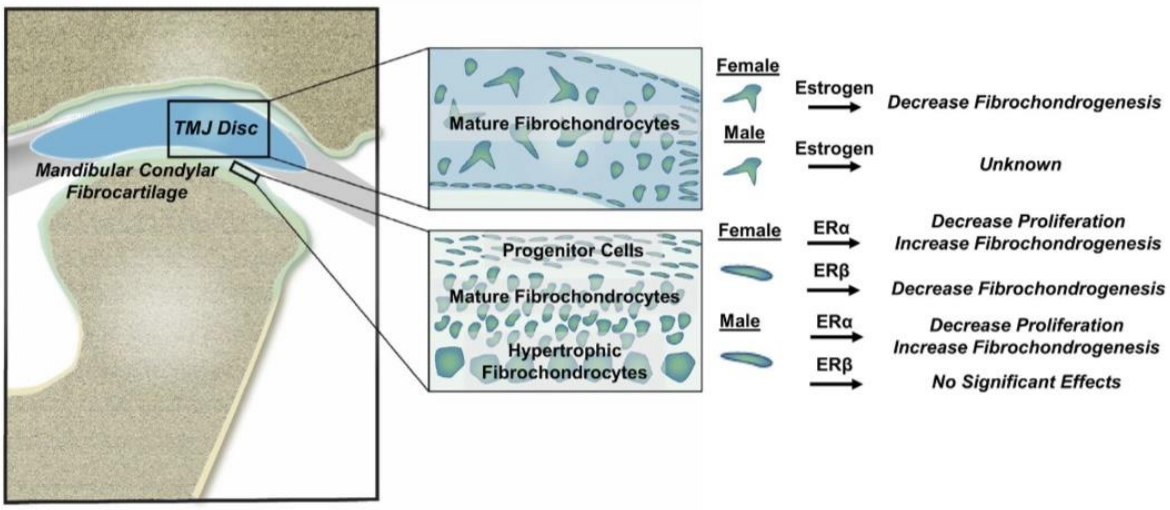

Figure:(1-3): Role of estrogen signaling via estrogen receptors alpha (ERα) and beta (ERβ) on cells from the temporomandibular joint disc and condylar fibrocartilage

1.3.2.4. The role of estrogen on periodontal diseases:

A. 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. However, the mechanism remains unclear. One way in which estrogen may potentiate gingivitis is by changing the composition of the oral microbiome [54]. 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 [55].

Estrogen-mediated effects are apparent in all major innate and adaptive immune cells, including neutrophils, macrophages, T cells and B cells. However, estrogen by itself does not seem to affect gingival crevicular fluid (GCF) cytokines levels [56]. For example, it was shown that rising estrogen levels during pregnancy did not affect IL-β or TNF-α levels. Furthermore, in another study they found that there was no difference in IL-1 α, IL-1 β, IL-8, TNF-α, and Secretory Leukocyte Protease Inhibitor (SLPI) mRNA levels in the (GCF) between samples from the 12th week of pregnancy and 4–6 weeks post-partum [57].

Pyogenic granuloma (PG), as it is a vascular tumor, includes angiogenesis as process acquires some growth factors and pro-angiogenic cytokines {vascular endothelial growth factor (VEGF)} and is regulated by an equally varied group of inhibitors (angiostatin) of neovascularization [58]. One of the most vital predisposing factors is puberty and pregnancy. The common resultant between them is the increase of the sexual hormones. (PG) during pregnancy affects the 5% of them, with both higher predilection for anterior gingiva of maxilla and new bone formation. In most cases, presents when a woman is pregnant in late first trimester, because of high levels of progesterone and poor oral hygiene and regresses after childbirth [59].

In order to be more specific, (PG) is the result of overproduction of (VEGF) and b-Fibroblast Growth Factor (bFGF) and decrease of angiostatin, thrombopsondin-1 and estrogen receptors. Progesterone and estrogens modify the answer to gingivitis and local irritations [60]. Estrogen enhances (VEGF) production in macrophages, an effect that is antagonized by androgens and which may be related to the development of pregnancy tumor [61].

B. Estrogen and periodontitis

The complex host immune response involves cells of both the innate and adaptive immune response as seen in (Figure:1-4). 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 (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) [(62)].

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 transforming growth factor beta (TGFβ) by osteoblasts, resulting in decreased osteoclast number and activity [(63)].

Estrogen deficiency after menopause enhances the production of TNFα and RANKL by T cells, increases production of osteoclast precursors and has both a pro-apoptotic effect on osteoblasts and an anti-apoptotic effect on osteoclasts as seen in (Figure:1-4). 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) [(64)].

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. However, a recent meta-analysis concluded that (HRT) in post-menopausal women did affect radiographic bone loss or clinical attachment loss. 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 [65].

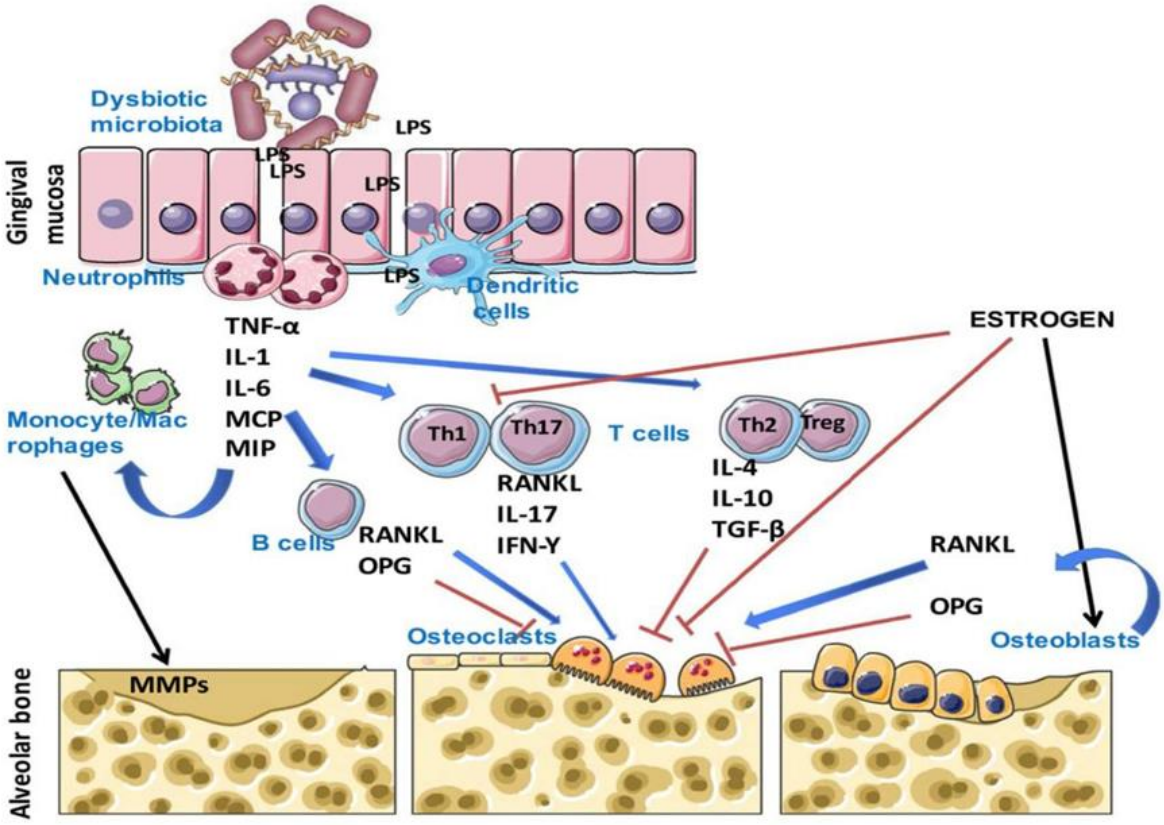

Figure:(1-4): Working model of potential role of estrogen in mediating periodontal disease-induced alveolar bone loss

Conclusion

Based on the available evidence from different researches, we conclude that: estrogen deficiency can trigger temporomandibular disorders by promoting the inflammation and bone resorption that result in disc inflammation, osteoarthritis, displacement, and condylar resorption in the temporomandibular joint. While the impact of estrogen deficiency on the periodontium induces gingivitis through its major effects on the innate and adaptive immune system and bone resorption that leads to periodontitis.

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