REVIEW ARTICLE

Effect of Androgens, Estrogens and Progesterone on Periodontal Tissues

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ABSTRACT

Hormones are specific regulatory molecules that have potent effects on the major determinants of the development and the integrity of the skeleton and oral cavity including periodontal tissues. Sex hormones have long been considered to play an influential role on periodontal tissues, bone turnover rate, wound healing and periodontal disease progression. This review focuses on the effects of endogenous sex hormones on the periodontium and the goal is to inform and update practitioners' knowledge about the impact of these hormones on periodontal status.

Keywords: Androgens, Hormones, Estrogen, Progesterone, Periodontium.

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INTRODUCTION

Hormones are specific regulatory molecules that modulate reproduction, growth, development and the maintenance of internal environments as well as energy production, utilization and storage.[1] Hormones can be classified into four groups based upon their chemical structure, including steroids, glycoproteins, polypeptides and amines.[2] Researchers have shown that changes in periodontal conditions might be associated with variations in sex hormone levels.

Sex hormones likely influence the pathogenesis of periodontal diseases.[3] This association is evident in the recent periodontal disease classification, which includes the following hormone-related disease categories: Puberty-associated gingivitis, menstrual cycle-associated gingivitis and pregnancy-associated gingivitis.[4] Therefore, the goal of this review paper is to discuss how sex hormones may influence the periodontium.

Steroid Sex Hormones

Steroid sex hormones are derived from cholesterol and as a common structure they have three rings of six carbon atoms. They are believed to play an important role in the maintenance of the skeletal integrity, including the alveolar bone. The steroid sex hormones, such as estrogen and estradiol have been known for their effect on bone mineral metabolism. Other bone turnover-related hormones include progesterone, testosterone and dihydrotestosterone, androstenedione, dihydroepiandrostenedione, and sex hormone-binding globulin.[5] Among these, estrogens, progesterone and androgen (testosterone) have been most linked with periodontal pathogenesis.

In women, estrogen and progesterone contribute to physiological changes at specific life phases. Puberty, menstrual cycle, pregnancy and menopause are all phases that specifically influence oral and periodontal health in women. Increased hormonal levels during puberty affect gingival tissues and the subgingival microflora.[6] For example, during puberty, *Prevotella intermedia* and *Capnocytophaga* bacterial species emerge.[7] Moreover, bleeding may occur when patients masticate or brush their teeth. In addition to puberty-induced changes, gingival tissues are more edematous during the menstrual cycle and erythematous before its onset. Consequently, increased gingival bleeding and exudation[8] has been observed during the menstrual period and is sometimes associated with slight increases in tooth mobility.[9]

Androgens (Testosterone)

Androgens are hormones responsible for masculinization. Testosterone can be produced in the adrenal cortex, although the one from the testes is the most active form.[10] Its secretion is regulated by ACTH and by pituitary adrenal androgen-stimulating hormone. The adrenal androgen androstenedione is converted to testosterone and to estrogens in the circulation and represents an important source of estrogens in men and in postmenopausal women. Specific receptors for this hormone have been isolated in the periodontal tissues.[11] Interestingly, the number of receptors in fibroblasts tends to increase in inflamed or overgrown gingiva. It is believed that an increasing matrix synthesis occurs on periodontal cells under testosterone influence.[12] Testosterone has also been associated with bone metabolism, playing a role in the maintenance of bone mass.[13] Kasperk et al observed that both gonadal androgen dihydrotesterone (DHT) and adrenal androgen dehydro-epiandrosterone (DHEA) have a positive impact on bone metabolism, by stimulating bone cell proliferation and differentiation.[14] A very effective way to analyze the effect of androgens on bone metabolism is the evaluation of the presence of biochemical markers of bone remodeling on bone tissue under the influence of those hormones. One of the bone remodeling markers that has been used for this objective is osteoprotegerin (OPG), which is a secreted decoy receptor

that inhibits osteoclast formation and activation by neutralizing its cognate ligand. This OPG action has been associated with a reduction in the loss of bone mineral density that is observed during periodontal disease progression.[15]

Effects of Androgens on the Periodontal Tissues

- Inhibit prostaglandin secretion[16]
- Enhance osteoblast proliferation and differentiation[13]
- Reduce IL-6 production during inflammation[17]
- Enhance matrix synthesis by periodontal ligament fibroblasts and osteoblasts.[18]

Estrogen and Progesterone

Estrogen and progesterone are responsible for physiological changes in women at specific phases of their life, starting in puberty. Estrogen induces several of the pubertal developmental changes in females, and progesterone acts synergistically with estrogen to control the menstrual cycle and to inhibit follitropin secretion by the anterior pituitary gland.[19] Specifically, estrogens can influence the cytodifferentiation of stratified squamous epithelium as well as the synthesis and maintenance of fibrous collagen.[19] Estrogen receptors found in osteoblast-like cells provide a mechanism for the direct action on bone. These receptors were also located in periosteal fibroblasts, scattered fibroblasts of the lamina propria[20] and periodontal ligament (PDL) fibroblasts,[21] proving the direct action of sex hormones on different periodontal tissues.

Effects of Estrogen on the Periodontal Tissues

- Decreases keratinization while increasing epithelial glycogen that results in the diminution in the effectiveness of the epithelial barrier[22]
- Increases cellular proliferation in blood vessels[23]
- Stimulates PMNL phagocytosis[24]
- Inhibits PMNL chemotaxis[25]
- Suppress leukocyte production from the bone marrow[26]
- Inhibits proinflammatory cytokins released by human marrow cells[26]
- Reduces T-cell mediated inflammation[27]
- Stimulates the proliferation of the gingival fibroblasts[26]
- Stimulates the synthesis and maturation of gingival connective tissues[28]
- Increases the amount of gingival inflammation with no increase of plaque.[29]

Effects of Progesterone on the Periodontal Tissues

- Increases vascular dilatation, thus increases permeability[30]
- Increases the production of prostaglandins[31]
- Increases PMNL and prostaglandin E2 in the gingival crevicular fluid (GCF)[32]
- Reduces glucocorticoid anti-inflammatory effect[33]
- Inhibits collagen and noncollagen synthesis in PDL fibroblast[34]
- Inhibits proliferation of human gingival fibroblast proliferation
- Alters rate and pattern of collagen production in gingiva resulting in reduced repair and maintenance potential[35]
- Increases the metabolic breakdown of folate which is necessary for tissue maintenance and repair.[36]

PERIODONTAL MANIFESTATIONS RELATED TO ENDOGENOUS SEX HORMONES

Puberty

Puberty marks the initiation of changes from maturation into adulthood.[37] It is associated with a major increase in the secretions of the sex steroid hormones: Testosterone in males and estradiol in females. Several cross-sectional and longitudinal studies have demonstrated an increase in gingival inflammation without accompanying an increase in plaque levels during puberty.[38]

There is a higher incidence of black-pigmented bacteroides and higher populations of other Gram-negative rods in the subgingival microflora compared with healthy sulci in puberty.[39] Especially, there is an increased prevalence of certain bacterial species, such as *Prevotella intermedia* and *Capnocytophaga* species.[40] Both estradiol and progesterone have been shown to selectively accumulate by *P.intermedia* as a substitute for vitamin K, and thus postulated to be acting as a growth factor for this microorganism.[41] *Capnocytophaga* species have also been noted to increase in number as well as proportion in the subgingival milieu during puberty and have been shown to correlate with an increased bleeding tendency.[40]

Clinical and Microbial Changes in the Periodontal Tissues during Puberty

- Increased gingival inflammation without accompanying an increase in plaque levels[39]
- Increased prevalence of certain bacterial species such, as *P. intermedia* and *Capnocytophaga* species.[11]

Menstruation

The onset of increased production, and secretion of estrogen and progesterone in a cyclic pattern accompanies the onset of puberty and is referred to as the reproductive or menstrual cycle. The duration of normal reproductive cycle is 28 days, and the monthly reproductive cycle has two phases.[42]

During the menstrual cycle, progesterone peaks at approximately 10 days (increases from the second week), and drops prior to menstruation.[43] Progesterone has been associated with increased permeability of the microvasculature, altering

the rate and the pattern of collagen production in the gingiva, increases folate metabolism, stimulates the production of prostaglandins and enhances the chemotaxis of polymorphonuclear leukocytes (PMNL).[44] As a result, significant gingival inflammatory changes have been documented in association with the menstrual cycle, and gingival inflammation seems to be aggravated by an imbalance and/or increase in sex hormones.[45] Bleeding and a swollen gingivae,[37,45,46] an increase in gingival exudates[40] and a minor increase in tooth mobility have all been demonstrated during menses.[45] A gradual increase in gingival fluid occurs during the proliferation phase just before menstruation,[46] where an increase in the production of estrogen and progesterone is observed. Nevertheless, most women with a clinically healthy periodontium experience few significant changes as a result of menstruation.

Clinical Changes in the Periodontal Tissues during Menstruation

- Bleeding and swollen gingiva[45]
- An increase in gingival exudates[47]
- A minor increase in tooth mobility.[45]

Pregnancy

Some of the most remarkable endocrine-related oral alterations occur during pregnancy due to increased plasma hormone levels. Progesterone and estrogen reach their peak plasma levels of 100 and 6 ng/ml respectively, by the end of the third trimester, and the potential biological impact of estrogen and progesterone take place in periodontal tissues during this period.[48]

Pregnancy gingivitis is extremely common occurring in a range between 30 and 100% of all pregnant women.[49] Pinard first described this situation in 1877 characterized with erythema, edema, hyperplasia and increased bleeding.[50] Cases range from mild inflammation to severe hyperplasia, pain and bleeding. Increased gingival probing depths, increased gingival inflammation, increased gingival crevicular fluid flow increased bleeding upon probing and increased tooth mobility[51] are the clinical periodontal manifestations that have been described during pregnancy. The anterior region of the mouth is more commonly affected and the interproximal sites tend to be the most involved areas.

Gingival inflammatory changes in pregnancy usually begin during the second month and the severity of the disease increases through the eight month, after which there is an abrupt decrease related to a concomitant reduction in sex steroid hormone secretion. Moreover, it has been confirmed that during pregnancy the severity of gingival inflammation is correlated to elevations of sex steroid hormones and is reduced following parturition and the concomitant drop-off in hormone production.[51] There is also an increased incidence of pyogenic granulomas during pregnancy at a prevalence of 0.2 to 9.6%.[37] The 'pregnancy tumor' or 'pregnancy-associated pyogenic granuloma' appears most commonly during the second or the third month of pregnancy. Gingiva is the most common site involved (70%) followed by tongue, lips, buccal mucosa and the palate.[52] The pregnancy tumor develops as a result of an exaggerated inflammatory response to local irritations, then enlarges rapidly and bleeds easily, and becomes hyperplastic and nodular. The tumor may be sessile or pedunculated and may range from purplish red to deep blue in color with small fibrin spots.

Increased sex steroid hormones have effects on gingival vasculature, subgingival microbiata, specific cells of periodontium and local immune system during pregnancy. Increased edema, erythema, gingival crevicular exudate and hemorrhagic gingival tissues may also be observed due to the effects of estrogen and progesterone on the gingival vasculature.[37,51]

Kornman and Loesche[53] reported that increased levels of estrogen and progesterone paralleled gingival conditions and the proportions of *P. intermedia* during pregnancy. During the second trimester, an increase in gingivitis and gingival bleeding without an increase in plaque levels have been reported and further a 55-fold of an increase in the proportion of *P. intermedia* has been reported in pregnant women compared to nonpregnant controls.[52]

Clinical and Microbial Changes in the Periodontal Tissues during Pregnancy

- Increased gingival probing depths[51]
- Increased gingival inflammation[54]
- Increased gingival crevicular fluid flow[51]
- Increased bleeding upon probing[55]
- Increased tooth mobility[45]
- Increased incidences of pyogenic granulomas
- Increased numbers of periodontopathogens especially *P. gingivalis* and *P. intermedia*.[53]

Menopause and Postmenopause

Menopause usually begins between 45 and 55 years of age unless accelerated by hysterectomy and/or ovariectomy.[37] The levels of estrogen begin to drop mainly during the late follicular and luteal phase of the menstrual cycle when women approach menopause.[56]

Katz and Epstein[5] suggested that peripheral conversion of androgens to estrogens might be the main factor for protecting bone since estrogens have inhibitory effects on osteoclastic functions. The postmenopausal period is associated with an

increased risk of osteoporotic fractures, myocardial infarction, menstrual cycle disorders, hot flushes, night sweats, vaginal dryness and possibly with an early onset of Alzheimer's disease.[57] The most significant problem that develops during menopause is osteoporosis.[37]

Osteoporosis is a worldwide disease characterized by low bone mass and fragility and a consequent increase in fracture risk. Osteoporosis is also responsible for less crestal alveolar bone per unit volume, a condition that may promote quicker bone loss when encountered with infections, such as periodontal infections.[58] Women may demonstrate menopausal gingivostomatitis and the clinical signs of this disease are drying of the oral tissues, abnormal paleness of the gingival tissues, redness and bleeding on probing and brushing.[59] Oral discomfort is also commonly reported by postmenopausal women with burning sensation, xerostomia and bad taste.

Clinical Changes in the Periodontal Tissues during Menopause and Postmenopause

- Reduction in epithelial keratinization[60]
- A reduction in salivary gland flow[61]
- Drying of the oral tissues[59]
- Redness and abnormal paleness of the gingival tissues[59]
- Bleeding on probing and brushing.[59]

Contraceptives

Hormonal contraceptives induce a hormonal condition that stimulates a state of pregnancy to prevent ovulation by the use of gestational hormones. Oral contraceptive agents are one of the most commonly used classes of drugs. The most commonly used contraceptives nowadays consist of low doses of estrogens (30 mg/day) and/or progestins (1.5 mg/day).[62-64] The influence of contraceptives on the periodontium is not limited to increases in inflammation and in the amount of gingival exudates.[65]

These drugs have also been associated with an increase in the prevalence of dry socket after dental extraction,[66] and accelerated progression of periodontal disease (higher gingival index scores and more loss of attachment) when they are used long-term. In contrast, some authors have found no significant influences on the periodontal clinical parameters when comparing oral contraceptives to nonmedicated control groups.[67]

Hormone Replacement Therapy in Postmenopausal Women

Osteoporosis, which is defined as a systemic condition characterized by a decrease in the bone mineral density of at least 2.5 times the normal values in a healthy young female, is a major health problem in postmenopausal women. In Western societies, more than one-third of the female population above the age of 65 years suffers from signs and symptoms of osteoporosis, a disorder characterized by low bone mass. Estrogen deficiency is the dominant pathogenic factor for osteoporosis in women. Although hormonal replacement in an adequate dosage can slow or prevent bone loss, only a small percentage of postmenopausal women receive such therapy, and many who do fail to comply with the prescribed regimen because of the fear of cancer, irregular bleeding and other minor side effects.[68] Progesterone alone is not effective in preventing postmenopausal bone and tooth loss, but when combined with estrogen it is believed to uncouple formation and resorption to diminish bone resorption induced by estrogen.[69] Paganini-Hill[70] analyzed the effects of estrogen replacement therapy (ERT) on the prevention of tooth loss and the need for dentures in older women. Results from this study indicated that the proportion of edentulous women decreased with increasing duration of ERT. It was concluded that ERT may be beneficial in preventing tooth loss and the need for dentures in older women. The available data indicates that hormone replacement therapy should be suggested for women during menopause since, several pathologic conditions common during this period of time can be avoided or at least reduced in severity.

CONCLUSION

Sexual hormones play an important role in influencing periodontal disease progression and wound healing. These effects are different depending on the gender as well as the lifetime period analyzed. It is also clear that not all patients and their periodontium respond in the same way to similar amounts of circulating sexual hormones. In addition, the influence of sex hormones can be minimized with good plaque control as well as with hormone replacement therapies; however, the true mechanism of how these interactions actually occur remains to be determined.

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