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REVIEW ARTICLE

SEX STEROIDS AND PERIODONTAL STATUS: A REVIEW

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ABSTRACT:
Sex hormones have long been considered to play an influential role on periodontal tissues, bone turnover rate, wound healing and periodontal disease progression. They play an important role in periodontal health and disease. For example, puberty, menses, pregnancy, menopause, oral contraceptive use in women periodontal health and hypogonadism in male periodontal health. Hormones are specific regulatory molecules that have potent effects on the major determinants of the development and the integrity of skeleton and oral cavity including periodontal tissues.
The purpose of this review paper is to brief the effects of endogenous sex hormones on periodontium.
Keywords: sex steroids, estrogen, progesterone, testosterone, cyto-differentiation, cytokines.

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INTRODUCTION

Bacterial plaque has been established asthe primary etiologic factor for theinitiation of periodontal disease.[1] However, it has also beenshown that without a susceptible hostthe periodontal pathogens are necessary but not sufficient for disease to occur.Periodontal disease results from a complex interplay betweenhost susceptibility and oral cavity microflora. Various systemicfactors and conditions of the host may affect the prevalence,progression, and severity of the disease.[2] Hence, the systemic factors/conditionsof the host must be understood sincethey may affect disease prevalence,progression, and severity.[3]

Among these, sexual hormones or sex steroids have been suggested as important modifyingfactors that may influence thepathogenesis of periodontal diseases.[4] Sex hormones alsoinfluence the onset and progression of periodontal diseases,[5] as hormonal variation affects the physiologyof host parasite interactions in the oral cavity [6].

Hormones are specific regulatory molecules that modulatereproduction, growth, and development. In addition, hormones maintain homeostasis, energy production, utilization and storage.[4]

Steroid Sex Hormones

Because of their complexity and diversity,hormones are difficult to arrangeinto discrete groups, although they canbe divided into four subgroups basedupon their chemical structure – steroids,

glycoproteins, polypeptides, and amines.Steroid sex hormones are derivedfrom cholesterol and as a commonstructure they have three rings of sixcarbon atoms. They are believed to playan important role in the maintenance ofthe skeletal integrity, including thealveolar bone. The steroid sex hormonessuch as estrogen and estradiol have beenknown for their effect on bone mineralmetabolism. Other bone turnover-related hormones include progesterone, testosterone and dihydro testosterone, androstenedione, dihydro epiandrostenedione, and sex hormone-binding globulin.[7] Amongthese, estrogens, progesterone, and testosteronehave been most linked withperiodontal pathogenesis.

Androgen, estrogen, and progesterone receptors are also localized in periodontal tissues.[8] Physiological/ pathological changes in almost all types of tissues of the body has been reported due to changes in hormonal levels. Receptors for a number of hormones such as androgens, estrogen, and progesterone have also been localized in periodontaltissues.[8] Consequently, systemic endocrine imbalances may have an important impact in periodontalpathogenesis.

Sex steroids have been linked to oral bone health. Estrogen use mayprovide protection against tooth loss in menopausal women[9]and testosterone may be related to periodontal health in hypogonadotrophic men.[10] Moreover, both estrogen and androgenmay have direct effects on the periodontium.[11] A variety of potential mmechanisms mightexplain the effects of sex steroids on periodontal disease, including modulationof immunological events.[12]

Female sex hormones and periodontium.

In women, estrogen and progesterone contributeto physiological changes at specific life phases. For example,estrogens can influence the cyto differentiation of stratified squamous epithelium, as well as the synthesis and maintenance offibrous collagen.[13] Progesterone exerts directefects on the periodontium and may play an important role inthe coupling of bone reabsorption and bone

formation.[14] Taken together, hormones influence a variety of tissues and may influencean individual's health.

Estrogen and Progesterone

Estrogen and progesterone are responsible for physiological changes in women at specific phases of their life, starting inpuberty. Estrogen induces several of thepubertal developmental changes in females,and progesterone acts synergisticallywith estrogen to control themenstrual cycle and to inhibit follitroppin secretion by the anterior pituitary gland.[6]Both hormonesare also known to promote proteinanabolism and growth.Both hormones have significant biologicalactions that can affect differentorgan systems including the oral cavity.[15] Specifically, estrogenscan influence the cytodifferentiation of stratified squamous epithelium as well as the synthesis and maintenanceof fibrous collagen.[6] Estrogen receptors foundin osteoblast-like cells provide a mechanismfor the direct action on bone.[16] These receptors were also located in periosteal fibroblasts,scattered fibroblasts of the laminapropria,[17] and periodontal ligament (PDL)fibroblasts, provingthe direct action of sex hormones ondifferent periodontal tissues.

Clinically, estrogen-sufficient patientshave been reported to have moreperiodontal plaque without increasedgingival inflammation when comparedto patients with deficient levels ofestrogens.[18] Thissuggests that inflammatory mediatorsmay be affected by estrogen hormonelevel, which may be attributed to theproduction of prostaglandins (PGs) bythe involvement of estradiol and progesterone.It is, therefore, speculatedthat normal circulating estrogen levelsmight be essential for periodontal protection.In fact, the amount of circulatingestradiol seems to be inverselycorrelated with the prevalence of periodontaldisease.[19]

Progesterone is another sex hormonethat has also been demonstrated to havedirect effects on the periodontium. Experimental, epidemiologic,and clinical data have demonstrated thatprogesterone is active in bone metabolismand may play an important role inthe coupling of bone resorption and bone formation. Studieshave shown that progesterone may exertits action directly on bone by engagingosteoblast receptors or indirectly bycompeting for a glucocorticoid receptors.[20]

Puberty, menstrual cycle, pregnancy, and menopause are allphases that specifically influence oral and periodontal health inwomen. Increased hormonal levels during puberty affect gingivaltissues and the subgingival micro flora.[21] For example, during puberty, Prevotella intermedia and Capnocytophaga bacteria species emerge.[22]

Clinically, there may be ahyperplastic reaction of the gingiva in those areas where localbacterial deposits are present. The inflamed tissues become deepred and may be lobulated, with ballooning distortion of theinterdental papillae. Histologically, tissue appearance is consistentwith inflammatory hyperplasia.[21]Moreover, bleeding may occur when patients masticate orbrush their teeth. In addition to puberty-induced changes, gingival tissues are more edematous during the menstrual cycleand erythematous before its onset. Consequently, increased gingival bleeding and exudation[23] has beenobserved during the menstrual period and is sometimes associated with slight increases in tooth mobility.[24] During pregnancy, progesterone and estrogen levelsare continuously elevated and, by the end of the third trimester,peak at 100 and 6 ng/ml, respectively. These hormone levels are10 and 30 times greater than the levels observed during themenstrual cycle. It is not surprising,then, that gingivitis is the most prevalent oral manifestationassociated with pregnancy and occurs within 30–100% of allpregnant women.[25] In additionto generalized gingival changes, localized gingival enlargements like ''pregnancy tumor,'' ''epulis gravidarum'' or ''pregnancy granuloma,'' are also observed. The hstological appearance is similar to a pyogenic granuloma, and the enlargement isfound in up to 9.6% of women.[8] Similartypes of gingival changes are also seen in women that are takingoral contraceptives.[24] Even during menopause, cwhen hormonal levels decline, women experiencechanges in the oral mucosa, which may result in burning sensations,altered taste perception, dryness of the mouth, or menopausal gingivostomatitis.[6]Several clinical and experimental studies have concludedthat subclinical infections in pregnant women are likely themost frequent cause of low births.[26] In the presence of periodontal disease, lipopolysaccharide exposure, inflammatory mediators, and cytokine productionin the maternal serum increase patient risk for poorpregnancy outcomes. Periodontal infection, as a chronic reservoirof lipopolysaccharides, may even target the placental membranesvia the bloodstream.[27]Therefore, periodontal disease not only influences women, it also affects pregnancy outcomes.

Table I Effects of estrogen in the Periodontium

- **increased amount of plaque with no increase of gingival inflammation inhibit proinflammatory cytokines release by human marrow cells**
- **reduce T-cell-mediated inflammation**
- **suppress leukocyte production from the bone marrow inhibit PMN chemotaxis**
- **stimulate PMN phagocytosis**

Table II: Effects of progesterone in the Periodontium
• increase production of prostaglandins(self-limiting process) • increase polymorphonuclear leukocytes and PGE2 in the GCF • reduce glucocorticoid anti-inflammatory effect • altered collagen and noncollageneous protein synthesis • alter PDL fibroblast metabolism • increase vascular permeability

Table III Clinical and microbiologic changes in the periodontiumduring puberty
• enhanced blood circulation in the end terminal capillary loops and associated increasedprevalence of gingivitis/bleeding tendency • higher bacterial counts (especially Prevotella intermedia (Pi) and Capnocytophaga species)

Table IV Clinical and microbiologic changes in the periodontium during pregnancy

• increased tendency for gingivitis and larger gingival probing depths • increased susceptibility to infection • decreased neutrophil chemotaxis and depressed antibody production • increased numbers of periodontopathogens (especially Porphyromonas gingivalis and Pi) • increased synthesis of PGE 2

Male sex steroids and periodontium

Androgens (testosterone)

Androgens are hormones responsiblefor masculinization. Testosterone canbe produced in the adrenal cortex,although the one from the testes is the most active form.[28] Its secretion is regulated by ACTH and bypituitary adrenal androgen-stimulatinghormone. The adrenal androgen androstenedione is converted to testosterone and to estrogens in the circulation and representsan important source of estrogensin men and in postmenopausal women.

Gonadal steroids have effects on skeletal biology in men. Hypogonadism is associated with bone loss and fracture risk,[29]and both estrogens and androgens affect bone mass in men.[30] With aging, estradioland testosterone levels decline in men, and reduced levels have been linked to bone loss.[31] Lower estradiol levels have been most clearly related to skeletal healthand are associated with lower trabecular bone mass, cortical thickness, corticaldensity, and trabecular thickness. As per the studies, it is reasonable that sex steroids may also affect oral bone metabolism, the likelihood of periodontal disease, and tooth loss.In fact, Despite this information, the relationship between periodontal health andsex steroid levels has not been examined in older men.[31]

Specific receptors for this hormonehave been isolated in the periodontaltissues.[32] Interestingly, the number of receptors infibroblasts tends to increase in inflamedor overgrown gingiva. It is believed that an increasingmatrix synthesis occurs on periodontalcells under testosterone influence.[33]Testosterone has also been associatedwith bone metabolism, playing a role inthe maintenance of bone mass.[34] A study performed on a group ofmen who were castrated for sexualoffences showed that bone densitysuffered a rapid decrease that was sustained for a number of years aftercastration.[35] it was also observed that both gonadal androgen dihydrotesterone (DHT) and adrenal androgen dehydro epiandrosterone (DHEA) have a positive impact onbone metabolism, by stimulating bonecell proliferation and differentiation. Avery effective way to analyze the effectof androgens on bone metabolism is theevaluation of the presence of biochemicalmarkers of bone remodeling onbone tissue under the influence of thosehormones.

One of the bone remodelingmarkers that has been used for this objective is osteoprotegerin (OPG),which is a secreted decoy receptor thatinhibits osteoclast formation and activationby neutralizing its cognate ligand.This OPG action has been associatedwith a reduction in the loss of bone mineral density that is observed duringperiodontal disease progression.[36]Author foundthat serum concentrations of OPGincreased significantly with age, andwere positively correlated with freetestosterone index and free estradiolindex. They concluded that age as wellas androgen and estrogen status aresignificant positive determinants,whereas parathyroid hormone (PTH) isa negative determinant of OPG serumlevels in men.[37] Thesedata suggest that OPG may be animportant paracrine mediator of bonemetabolism in elderly men and highlightthe role of androgens in thehomeostasis of the male skeleton.Studies have also examined how thefunction of these hormones is controlledor regulated in the periodontium, lookingspecifically at the influence ofdifferent growth factors on the stimulationof DHT synthesis. Authors found significant stimulation ofDHT synthesis by insulin-like growthfactor (IGF) in gingiva and culturedfibroblasts.[38] This finding suggests apossible mechanism of mediating inflammatoryrepair via the androgenmetabolic pathway. The same authorslater investigated the effects of interleukin-1 (IL-1) on the metabolism ofandrogens from chronically inflamedhuman

gingival tissue (HGT) andPDL. In response to IL-1, HGT demonstrateda two-fold increase in DHTsynthesis and a 3.5-fold increase in 4-androstenedione formation over controlgingival tissue; the PDL showed a 9-fold increase in DHT synthesis inresponse to IL-1 and a 6-fold increasein 4-androstenedione formation overcontrol ligament tissue. The observationof increased androgen metabolic capacityof PDL over HGT in response toIL-1 insult might be relevant to repairprocesses during inflammatory periodontaldisease. Androgens also have a reciprocaleffect on other important mediators ofinflammation, more specifically on IL-6.This cytokine plays a major role intissue damage during periodontal diseases,and is secreted by many celltypes, including oral fibroblasts.

Using ELISA, they observed that increasingDHT concentrations progressivelyreduced IL-6 production bygingival cells from both normal individualsand patients with gingival inflammationand gingival hyperplasia.[39]It was found androgen receptors to bepresent in both human gingival andperiodontal ligament fibroblasts, andreduced the production of IL-6 in thepresence of androgens.[8] It was suggestedthat elevated levels of androgens, more specifically testosterone and dihydrotestosterone, could affect the stromal cellresponse to an inflammatory challenge through down regulation of IL-6 production. An in vitro study analyzed therelationship between various concentrationsof male testosterone and theformation of radioactive PGs from arachidonic acid by gingival homogenate.[40]They reportedthat testosterone had inhibitory effectsin the cyclooxygenase pathway of arachidonic acid metabolism in thegingiva, and speculated that this sexhormone may have anti-inflammatoryeffects in the periodontium. Thesesteroids can exert an anabolic effect onthe tissues even when their anaboliccapacity is decreased, as is the caseduring inflammation. These findingssupport the concept that androgensmay have a limiting effect on periodontalinflammation during periodontaldisease progression. From the researchreported above, it can be concluded thatthe production of androgens is stimulatedby the presence of proinflammatory cytokines commonly found on periodontally diseased tissues and is down regulated by proinflammatory cytokinesconcentration as well as theconcentration of prostaglandins.Overall, androgensmay protect the periodontium via apositive anabolic effect on periodontalcells, a negative effect on the productionand presence of mediators of inflammation,and an inhibitory effect on osteoclastic function.

Table V Effects of androgens in the periodontium

- **stimulate matrix synthesis by osteoblasts and periodontal ligament fibroblasts**
- **stimulate osteoblast proliferation and differentiation**
- **reduce IL-6 production during inflammation**
- **inhibit prostaglandin secretion**
- **Enhance OPG concentration**

CONCLUSION

Sex hormones are neither necessary nor sufficient to produce gingival changes by themselves. However, they may alter periodontal tissue responses to microbial plaque and thus indirectly contribute to periodontal disease.

Various studies have shown that changesin periodontal conditions might be associatedwith variations in sex hormonelevels. This association is evident in therecent periodontal disease classification,[41] which includes thefollowing hormone-related disease categories:puberty-associated gingivitis,menstrual cycle-associated gingivitis andpregnancy-associated gingivitis. Therefore, the aim of this review paper was todiscuss how sex hormones may influencethe periodontium and periodontal wound/bone healing.

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