

# Effect of menopause on women's periodontium

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## ABSTRACT

Steroid sex hormones have a significant effect on different organ systems. As far as gingiva is concerned, they can influence the cellular proliferation, differentiation and growth of keratinocytes and fibroblasts. Estrogen is mainly responsible for alterations in blood vessels and progesterone stimulates the production of inflammatory mediators. In addition, some micro-organisms found in the human mouth synthesize enzymes needed for steroid synthesis and catabolism. In women, during puberty, ovulation, pregnancy, and menopause, there is an increase in the production of sex steroid hormones which results in increased gingival inflammation, characterized by gingival enlargement, increased gingival bleeding, and cervicular fluid flow and microbial changes.

**Key Words:** Gingiva, menopause, periodontium, steroid sex hormones, women

## INTRODUCTION

The main sex hormones exerting influence on the periodontium are estrogen and progesterone. Estrogen and progesterone can significantly influence different organ systems.<sup>[1,2]</sup> For example, estrogens can influence the cytodifferentiation of stratified squamous epithelium, and the synthesis and maintenance of fibrous collagen.<sup>[3]</sup> Additionally, estrogen receptors in osteoblast-like cells provide a mechanism for direct action on bone while estrogen receptors in periosteal fibroblasts and periodontal ligament fibroblasts provide a mechanism for direct action on different periodontal tissues.<sup>[1]</sup> Estrogen, progesterone, and chorionic gonadotropin, during pregnancy, affect the microcircularity system by producing the following changes: swelling of endothelial cells and pericytes of the venules, adherence of granulocytes and platelets to vessel walls, formation of microthrombi, disruption of the perivascular mast cells, increased vascular permeability and vascular proliferation.<sup>[4-7]</sup> Currently accepted periodontal disease classification recognizes the influence of endogenously produced sex hormones on the periodontium. Under the broad category of dental plaque induced gingival diseases that are modified by systemic factors, those associated with the endocrine system are classified as puberty, menstrual cycle and pregnancy associated gingivitis. Researchers have shown that changes in periodontal conditions may be associated with variations in sex hormones. Therefore,

this review will focus on the effects of endogenous sex hormones on the periodontium to update practitioners' knowledge about the impact of these hormones on periodontal status.<sup>[8]</sup>

## MECHANISMS OF ACTION OF SEX STEROID HORMONES ON GINGIVA OF WOMEN

Sex steroid hormones have been shown to directly and indirectly exert influence on cellular proliferation, differentiation and growth in target tissues, including keratinocytes and fibroblasts in the gingiva.<sup>[2,9]</sup> There are two theories for the actions of the hormones on these cells: a) change of the effectiveness of the epithelial barrier to bacterial insult and b) effect on collagen maintenance and repair. Estradiol can induce cellular proliferation while depressing protein production in cultures of human premenopausal gingival fibroblasts. This cellular proliferation appears to be the result of a specific population of cells within the parent culture that responds to physiologic concentrations of estradiol.<sup>[10]</sup> In contrast to the stimulatory effects of estrogen on gingival fibroblast proliferation, both collagen and noncollagen protein production were reduced when physiological

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concentrations of estradiol were introduced to fibroblasts in culture. The reductions of collagen and noncollagen protein production by fibroblast strains were similar (approximately 30% reduction in comparison to controls); therefore, there was no effect of estrogen on the relative amount of collagen synthesized by gingival fibroblasts. Similar effects of estrogen on protein synthesis have also been reported in other tissues. In human periodontal ligament cells, estrogen triggered an *in vitro* reduction in fibroblast collagen synthesis.<sup>[11]</sup> Furthermore, fibroblasts derived from human anterior cruciate ligament have also exhibited a reduction of collagen synthesis by more than 40% of controls at physiological concentrations of estrogen.<sup>[12]</sup> More specifically, estrogen induced a dose dependent decrease in the production of procollagen I from anterior cruciate ligament fibroblasts<sup>[13]</sup> of young adult women. Sex steroid hormones have also been shown to increase the rate of folate metabolism in oral mucosa.<sup>[14]</sup> Since folate is required for tissue maintenance, increased metabolism can deplete folate stores and inhibit tissue repair.<sup>[9]</sup>

Estrogen is the main sex steroid hormone responsible for alterations in blood vessels of target tissues in females, stimulating endometrial blood flow during the estrogen plasma rise seen in the follicular phase. Subsequently, endometrial blood flow decreased during the luteal phase of the cycle with waning estrogen levels.<sup>[15]</sup> In contrast, progesterone has been shown to have little effect on the vasculature of systemic target tissues.<sup>[9]</sup> On the other hand, in gingiva and other nonperiodontal intraoral tissues, more evidence has accumulated for progesterone affecting the local vasculature than for estrogen. In addition, progesterone has been shown to reduce corpuscular flow rate, allowing for accumulation of inflammatory cells, increased vascular permeability and proliferation.<sup>[16-19]</sup> Human PDL cells possessed immunoreactivity for (toward) estrogen receptors. More specifically estrogenic effects in PDL cells are mediated via estrogen receptors beta (ERbeta), whereas no immunoreactivity was expressed in these cells for progesterone receptors, which implies that progesterone does not have a direct effect on PDL cell function.<sup>[20]</sup>

These hormones may alter immunologic factors and responses, including antigen expression and presentation, and cytokine production, as well as the expression of apoptotic factors, and cell death.<sup>[21]</sup> Several studies have focused on the observation that immune system components have been identified as possessing sex steroid receptors.<sup>[9]</sup> In mice, the presence of oestrogen receptors on various immune cells has been demonstrated, as well as the presence of androgen receptors on T and B lymphocytes.<sup>[22]</sup> Progesterone in particular has been shown

to stimulate the production of the inflammatory mediator, prostaglandin E2 and to enhance the accumulation of polymorphonuclear leukocytes in the gingival sulcus.<sup>[23]</sup> Progesterone has also been found to enhance the chemotaxis of polymorphonuclear leukocytes, while low concentrations of estradiol have been demonstrated to reduce polymorphonuclear leukocytes chemotaxis.<sup>[24]</sup> In addition, sex steroid hormones seem to modulate the production of cytokines,<sup>[25]</sup> and progesterone has been shown to downregulate Il-6 production by human gingival fibroblasts to 50% of that of control values.<sup>[26,27]</sup> According to a radically new insight into the diversity of human oral microflora, the human mouth consists of an estimated number of 19 000 phylo types, which is considerably higher than previously reported.<sup>[28]</sup> Although the hypothesis that hormonal changes in the menstrual cycle cause changes in the oral microbiota could not be confirmed.<sup>[29]</sup> Some micro-organisms, such as *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Prevotella intermedia*, are known to synthesize steroid metabolizing enzymes needed for steroid synthesis and catabolism.<sup>[30]</sup> The steroid metabolites may also contribute to nutritional requirements of the pathogens, or enable synthesis of matrices associated with host evasion mechanisms.<sup>[31]</sup> The need for an androgen metabolic pathway in pathogens may be an adaptation to a parasitic presence in the host. Culture supernatants of these micro-organisms have been shown to enhance the expression of 5a-reductase activity in human gingiva and in cultured gingival fibroblasts, resulting in the formation of 5a-dihydrotestosterone (DHT) from androgen substrate.<sup>[32]</sup> The DHT can influence protein synthetic activity in these pathogens, for which there is a variety of applications. Some of these functions are: (a) the formation of surface capsular protein contributing to their evasion of host elimination mechanisms, such as phagocytosis, by preventing opsonisation, (b) persistence and dissemination with the host, and (c) interspecies aggregation and energy generation as a result of the electron transfers involved in these enzyme activities.<sup>[31]</sup> 5a-reductase activity can be activated in a phospholipidic environment. Increased amounts of phospholipases A2 and C are synthesized by periodontal pathogens (e.g., spirochaetes) during inflammatory episodes in the periodontium. Phospholipase C is also released from leukocytes during cell lysis and in addition to degrading gingival crevicular epithelium it is also known to stimulate 5a-reductase activity.<sup>[32]</sup>

## INFLUENCE OF MENOPAUSE ON PERIODONTIUM

The menopause and the lack of ovarian steroids are known to promote important changes in connective tissue.<sup>[33]</sup> The mechanisms involved in this influence are not completely understood, but it is thought to be related to the action

of estradiol on the connective tissue.<sup>[34]</sup> The menopause triggers a wide range of changes in women's bodies, and the oral cavity is also affected. Although elevated levels of ovarian hormones, as seen in pregnancy and oral contraceptive usage, can lead to an increase of gingival inflammation with an accompanying increase in gingival exudates,<sup>[35]</sup> conversely, the menopause – the absence of ovarian sex steroids – has been related to a worsening in gingival health, and hormonal replacement therapy seems to ameliorate this trend.<sup>[36]</sup> Studies have shown that use of depot medroxyprogesterone acetate (DMPA) injectable contraception may be associated with periodontal diseases in women.<sup>[37]</sup> An increase in gingivitis, periodontal disease, tooth loss and dry mouth has been reported<sup>[38]</sup> and hormone replacement seems to be associated with decreased levels of several indicators of the severity of oral disease as compared with estrogen-insufficient women.<sup>[39,40]</sup> During the menopause estrogen deficiency is one of the most frequent causes of osteoporosis in women and a possible cause of bone loss and insufficient skeletal development in men. Estrogen plays an important role in the growth and maturation of bone as well as in the regulation of bone turnover in adult bone. During bone growth estrogen is needed for proper closure of epiphyseal growth plates both in females and in males. Also in the young skeleton estrogen deficiency leads to increased osteoclast formation and enhanced bone resorption. In menopause estrogen deficiency induces cancellous as well as cortical bone loss. Highly increased bone resorption in cancellous bone leads to general bone loss and destruction of local architecture because of penetrative resorption and microfractures. In cortical bone the first response of estrogen withdrawal is enhanced endocortical resorption. Later, also intracortical porosity increases. These lead to decreased bone mass, disturbed architecture and reduced bone strength.<sup>[41]</sup> Estrogen may play an important role in exerting anti-resorptive effects on alveolar bone, at least in part, by increasing the expression level of osteoprotegerin.<sup>[42]</sup> The mechanism by which estrogen deficiency causes bone loss remains largely unknown. Estrogen deficiency leads to an increase in the immune function, which culminates in an increased production of TNF by activated T cells. TNF increases osteoclast formation and bone resorption both directly and by augmenting the sensitivity of maturing osteoclasts to the essential osteoclastogenic factor RANKL. Increased T cell production of TNF is induced by estrogen deficiency via a complex mechanism mediated by antigen presenting cells and involving the cytokines IFN-g, IL-7, and TGF-b. Experimental evidence suggests that estrogen prevents bone loss by regulating T cell function and immune cell bone interactions. Remarkable progress has been made in elucidating the crosstalk between the immune system

and bone, and in uncovering the mechanism by which sex steroids, infection, and inflammation lead to bone loss by disrupting the regulation of the T lymphocyte function in animal models. If the findings in experimental animals are confirmed in humans, it will, perhaps, be appropriate to classify osteoporosis as an inflammatory, or even an auto-immune condition and certainly new therapeutic “immune” targets will emerge.<sup>[43]</sup>

## **BONE - SPARING AGENTS FOR PREVENTION OF BONE LOSS**

During the past 10 years, the use of bisphosphonate bone-sparing agents has been incorporated in the management of osteoporosis and other bone-resorptive diseases.<sup>[44]</sup> Bisphosphonates are widely utilized in the management of systemic metabolic bone disease due to their ability to inhibit bone resorption. Recently, new uses of this unique class of pharmacological agents have been suggested. Given their known affinity to bone and their ability to increase osteoblastic differentiation and inhibit osteoclast recruitment and activity, there exists a possible use for bisphosphonates in the management of periodontal diseases.<sup>[45]</sup> Data suggest that bisphosphonate treatment improves the clinical outcome of nonsurgical periodontal therapy and may be an appropriate adjunctive treatment to preserve periodontal bone mass.<sup>[46]</sup> Treatments of periodontal diseases in postmenopausal women with oral Alendronate have shown improved periodontal status and more bone turnover.<sup>[47]</sup> Risedronate therapy in women have shown significantly less plaque accumulation, less gingival inflammation, lower probing depths, less periodontal attachment loss, and greater alveolar bone levels.<sup>[48]</sup> Healthcare professionals should be aware that systemic bone conditions impact the periodontium. Bisphosphonate drugs used for systemic bone loss affect the maxilla and mandible. Alveolar bone loss in periodontitis and skeletal bone loss share common mechanisms. At present, bisphosphonates are in wide use for prevention and treatment of osteoporosis, Paget's disease and metastatic bone conditions. At the same time, bisphosphonate therapy is also reported to be beneficial to the periodontium. In fact, periodontal therapy using bisphosphonates to modulate host response to bacterial insult may develop into a potential strategy in populations in which periodontal therapy is not convenient. Unlocking the full potential of bisphosphonates involves understanding the mechanisms of action of different classes of bisphosphonates, limiting unwanted side effects and expanding its indications. Developing bisphosphonates to slow the progression of periodontal disease depends on identifying an effective dosage regimen and delivery system that would reach the target site in the periodontium, while limiting unwanted side effects.<sup>[49]</sup>

## CLINICAL SIGNIFICANCE

Buencamino and colleagues reviewed the association between menopause and periodontal disease. They suggested that postmenopausal women can be managed, in part, by returning to the basics suggested by the ADA:<sup>[50]</sup>

- Regular dental examinations; regular professional cleaning to remove bacterial plaque biofilm under the gum-line where a toothbrush will not reach.
- Daily oral hygiene practices to remove biofilm at and above the gum-line including brushing twice daily with an ADA-accepted toothpaste.
- Replacing the toothbrush every 3–4 months (or sooner if the bristles begin to look frayed).
- Cleaning interproximally (between teeth) with floss or interdental cleaner.
- Maintaining a balanced diet.
- No smoking.

Researchers also suggested that postmenopausal women should maintain an adequate vitamin D status in order to prevent and treat osteoporosis-associated periodontal disease.<sup>[51]</sup>

## CONCLUSION

Female 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.

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