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# THE ASSOCIATION BETWEEEN ESTROGEN AND PERIODONTAL DISEASE IN ADULT WOMEN

# ОДНОСОТ ПОМЕЃУ ЕСТРОГЕНОТ И ПАРОДОНТОПАТИЈАТА КАЈ ВОЗРАСНИ ЖЕНИ

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## Abstract

Literature supports the fact that estrogen plays an important role in skeletal maintenance and remodeling. Estrogen, acting through estrogen receptors in the cells of the periodontal ligament, has a regulatory interaction on bone dynamics through a complex set of basic multicellular units (BMUs). Deficiency of estrogen results in an increased number of BMUs and enhanced bone turnover. The impact of the changes in estrogen deficiency on bone dynamics is primarily mediated through osteoclasts, with greater interdiction of estrogen's actions on trabecular bone than on cortical bone. The purpose of this manuscript is to review literature for evidence to support the association between estrogen and periodontal disease in adult women, as well as bone mineral density, and to help clarify the mechanism of action. Key words: Estrogen, periodontal disease, bone, adult women, receptors.

## Апстракт

Литературата го поддржува фактот дека естрогенот игра важна улога во скелетното одржување и ремоделирање. Естрогенот, дејствувајќи преку естрогенските рецептори во клетките на пародонталниот лигамент, има регулаторна интеракција во динамиката на коските преку комплексен сет на основни мултицелуларни единици(БМУ). Недостаток на естроген резултира во зголемен број на БМУ и зголемен обрт на коските. Влијанието на промените во недостатокот на естроген првенствено се посредува преку остеокластите и тоа повеќе на трабекуларната отколку на кортикалната коска. Целта на овој труд е да се разгледаат литературните податоци за асоцијацијата помеѓу естрогенот и пародонталната болест кај возрасни жени, како и густината на коската и механизмот на дејствување. Клучни зборови: естроген, пародонтална болест, коска, возрасни жени, рецепотри.

## Introduction

Periodontal disease is observed more frequently in postmenopausal women whose menopausal status has been altered either surgically or as a side effect of chemotherapy. Oral bone loss may also be an indicator of periodontal disease[1,2]. However, the specific nature of the relationship between estrogen levels and periodontal disease is still being investigated. It suggested that women who were post-antineoplastic therapy had a higher plaque index, increased gingival inflammation and bleeding upon probing compared to healthy controls. With regard to periodontal disease, the weighted prevalence of severe gingivitis was 20.3% higher compared to the healthy control group[1]. Most chemotherapeutic agents affect estrogen levels by causing the death of ovarian cells. This is a result of the cytostatic effect of chemotherapy agents. These drugs prevent cell division of cancer cells and prevent cellular mitosis. However, normal cells are also killed, especially sensitive reproductive cells in the ovaries. This is known as "chemotherapy induced ovarian failure" which, in turn, causes a large decrease in estrogen that affects changes in bone mineral density. These changes are mediated by estrogen receptor alpha (ERa) and estrogen receptor beta (ERb.) Estrogen receptors are found in all layers of the gingival epithelium, buccal mucosa and salivary glands. Estrogen receptors exist as two subtypes: estrogen receptor alpha (ERa) and (ERb)[3].

Some research articles have shown that ERa was completely undetected in oral tissues, whereas ERb was expressed in high levels in oral epithelium and salivary glands[4,5]. The differential expression of ERb in these tissues may account for the conflicting results in estrogen receptor expression in earlier studies. In this study, the results show that a tissue-specific subtype distribution is also observed in oral tissues with ERb but not ERa. ERa is usually expressed in classic target tissues, such as breast tissue. The identification of ERb in these tissues has significant clinical importance and suggests a direct role for estrogen in the physiology of the oral mucosa and salivary gland function[4]. Forty percent of these cells demonstrate ERb immunoreactivity.

In a study by Pan, Zhang et al.[4], both estrogen receptors, ERa and ERb, have been detected in periodontal ligament cells (PDLCs). And both receptors have been shown to stimulate the bone formation capacity of cultured PDLCs by increasing alkaline phosphatase (ALP) activity, osteocalcin distribution and formation of mineralized nodules[6,7]. These compounds are markers for bone formation.

ALP activity was much higher in the estrogen-treated periodontal ligament stem cells (PDLSCs) than in the control group[6]. Additionally, in the estrogen-treated groups, the ALP activity was stimulated in a dose-dependent manner. The higher expression of ERa and ERb in PDLSCs as compared to PDLCs indicates a potential involvement of ERa and ERb in the process of estrogeninduced osteogenic differentiation of PDLSCs[8].

Evidence suggests that insufficient estrogen levels are a major cause of osteopenia and postmenopausal osteoporosis. Metabolic diseases that may also affect the levels of estrogen include hyperparathyroidism, hypopituitarism, Cushing's disease, adrenal insufficiency, rheumatoid arthritis and malignant disease. Several studies suggest that osteoporosis is a risk factor for periodontal disease and tooth loss[2-5,7]. Cells of the periodontal ligament are capable of producing all of the structures of the attachment apparatus. They can differentiate into osteoblasts (bone formation), cementoblasts (cementum formation) and fibroblasts (collagen formation)[8-10]. These cells also modulate the production of osteoclasts, which induce the breakdown of bone[5,8]. Estrogen plays a regulatory role in maintaining the balance between osteoblast production and osteoclast production. This role of estrogen is vital to maintaining normal bone mass and bone density. Thus, a relationship between estrogen levels and periodontal disease is plausible.

During menopause, the onset of ovarian deficiency (resulting in a decrease in estrogen levels) affects bone mass density (BMD). Normal loss of BMD is 0.7 percent per year during menopause. This may be explained by the inhibition of the down-regulating effects of osteoclasts, resulting in increased bone breakdown unlike bone apposition[8,11]. Other effects include loss of keratin, thinning of gingival tissues, redness, soreness and decreased salivary gland function. Estrogen can also modulate the pathogenicity of periodontal pathogens, such as P. Gingivalis and P. Intermedia; and it is reasonable to expect that its reduction may imply more severe periodontitis.

A study by Bin Zhang, Ying Li, et al.[12], utilizing ovariectomized rats with induced periodontitis and a SHAM control, explored the effect of estrogen on the potential for osteogenic differentiation of periodontal ligament stem cells. The results showed there was a lower expression of estrogen receptors (ERa and ERb) in the ovariectomized group than the sham group. Treatment with 17beta estradiol significantly increased osteogenic differentiation of PDLSC in both groups in vitro. The results seem to indicate that estrogen plays an important role in maintaining osteogenic differentiation of periodontal stem cells, which act through ERa and ERb[3].

Evidence suggests that "estrogen deficiency leads to impaired osteogenic differentiation of periodontal stem cells in rats"[12,14-16].

Stossi et al.[4] demonstrated that both ERa and ERb transcriptionally up-regulated bone morphogenic protein-6 (BMP-6), a key factor in bone formation. This supports the findings of the present study by Feng Pan, Zhang, et al.[4] that both ERa and ERb may function in the osteogenic differentiation of periodontal stem cells. This difference may be explained by the fact that in the different types of cells, the varied expression patterns of ERa and ERb are under the control of specific mechanisms. Investigators have also considered the role of a variety of inflammatory cytokines and growth factors and the effect of estrogen on the gingival fibroblast. Cytokines, such as interleukins and interferons, are substances that are produced by specific cells of the immune system and have an immune modulating effect and are critical to the functioning of the immune system[14].

Estrogen may suppress osteoclastogenesis by modulating the synthesis of cytokines produced locally by human PDLCs. There is now convincing evidence that estrogen, acting through ERa, stimulates osteoclast apoptosis 16 and, conversely, suppresses osteoblast and osteocyte apoptosis. Therefore, estrogen deficiency is associated with an increase in the lifespan of osteoclasts, as well as a concomitant decrease in the osteoblastic lifespan[15].

During the postmenopausal process, women lose 30% to 50% of the trabecular bone and 25% to 35% of the cortical bone mass that was present during the peak bone mass years between ages 20 to 30 (normal bone loss averages 0.7% per year)[17]. Postmenopausal women with osteoporosis and concurrent periodontitis may show a loss of dentoalveolar bone height and decreased BMD of the alveolar crestal and subcrestal bone[17].

Clinical research by Atkinson et al.[18] demonstrated a reduction in bone mineral content between six and nine months after MTX treatment (methotrexate, cytostatic drug and, thus, lowers estrogen production). It is unknown whether the bone mass remains depressed indefinitely, slowly recovers to normal levels or recovers to osteopenic levels below the normal range. It is known that one course of methotrexate therapy will induce osteopenia and depress bone formation 14 days following treatment[18].

Friedlander et al.[19,20] also reported significant reduction (27%) in cancellous bone volume after one course of methotrexate. There is an important association between loss of bone mass and periodontal disease.(21) Kribbs showed there was a significant correlation between skeletal bone mass measurements and the number of remaining teeth[21].

Yoshihara et al. and Klemetti et al. showed that the BMD of the mandible is affected by the mineral status of the skeleton and by any disease that causes generalized bone loss[22]. Ward and Manson were able to find an association between the periodontal disease index and alveolar bone loss[23].

Groen et al. assessed the relationship between osteoporosis or low bone density and clinical attachment loss. Toothlessness and severe periodontal disease were found in 38 patients aged 43 to 73 who exhibited clinical and radiographic signs of advanced osteoporosis[24]. Most studies showed a correlation between reduced bone mineral density and increased severity of periodontal disease.

The findings from the Women's Health Initiative (W.H.I.) on 42,171 postmenopausal women showed the overall risk of tooth loss was 24% lower in current hormone replacement therapy (HRT) users when compared to nonusers. Furthermore, the results showed that estrogen may promote tooth retention by strengthening the periodontal attachment surrounding the teeth, without increasing oral bone height or decreasing oral bone porosity.

Tagutchi et al.[25] and Grossi[26] further showed that women who were not treated with estrogen replacement therapy (ERT) were twice as likely as their ERT counterparts and three-times more likely than premenopausal women to exhibit severe attachment loss. The individual percentages of women affected by severe attachment loss were 18.6%, 11.9% and 6.3% for non ERT, ERT and premenopausal women, respectively. Also, severe alveolar bone loss (ABL) was detected in 34%, 20.3% and 9.7% of the non-ERT, postmenopausal ERT, and premenopausal women, respectively. The authors, therefore, concluded that ERT appears to have a protective effect on the severity of periodontal disease and the periodontium[26]. The duration of estrogen use was significantly associated with the number of remaining teeth.

## Discussion

At this time, a thorough review of all databases revealed there are few studies that provide evidence of the direct association between estrogen deficiency, and periodontal disease and between BMD and periodontal disease. Furthermore, there are no prospective observational studies to assess estrogen as a risk factor for periodontal disease that account for confounding factors such as age, socioeconomic status, nutrition, smoking and health status.

Clinicians have found that "HRT (hormone replacement therapy) can improve the clinical outcome of periodontal disease and may serve as an effective adjunct treatment for preserving periodontal bone mass"[4].

Despite these limitations, there is evidence to suggest an association between estrogen and periodontal disease, because estrogen receptors are found in the cells of the periodontal ligament, gingiva, salivary glands and jaw bone. Estrogen has an effect on these tissues and exerts its effect locally. These effects include maturation of gingival connective tissue, osteoblastic differentiation and mineralization. Estrogen deficiency will alter skeletal remodeling and, thus, affect bone mass density, and bone volume.

## Conclusion

Estrogen, acting through ERa and ERb located in the cells of the periodontal ligament, may have a significant impact on the periodontium. Estrogen receptors have a regulatory effect on both the maturation of gingival epithelium and on the osteoblastic differentiation of periodontal ligament cells. ERb may play an important role in bone formation.

Estrogen deficiency may result in osteoporosis, which is considered to be a risk factor for periodontal disease, loss of BMD and tooth loss. Both disease processes share common risk factors, are inflammatory in nature, and are bone-resorptive entities.

Further research is necessary to establish better associations between periodontal disease, estrogen and bone mineral density, so that at-risk patients can be identified earlier to avoid the functional and esthetic sequellae of periodontal disease.

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