

The Effects of Menopause on Periodontal Tissue

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Abstract

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Periodontitis and gingivitis, a prevalent oral diseases, have been connected to several systemic health changes. The aim of this investigation was to review the effects of menopause on periodontal tissue. Epidemiologic studies have identified a number of risk factors and risk indicators for periodontal attachment loss, including demographic, socioeconomic, behavioural, genetic, and systemic factors. Menopause has also been associated with destructive periodontal disease in older women. The homeostasis of the periodontium involves complex multifactorial relationships. Oestrogen and progesterone are responsible for physiological changes in women at specific phases of their life. Menopause is associated with significant adverse changes in the orofacial complex.

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Periodontal disease refers to both gingivitis and periodontitis. Gingivitis is an inflammatory condition of the soft tissues surrounding the teeth. The main symptoms of gingivitis are redness, swelling and bleeding of gums. Gingivitis can often be controlled by removing the hard and soft deposits from the tooth surface (1). If unchecked, gingivitis progresses to periodontitis, an inflammation of the supporting tissues of the teeth, including the gingiva, alveolar bone, and periodontal ligament (2). Periodontitis is a chronic inflammatory process that occurs in response to a predominantly Gram-negative bacterial infection originating in dental plaque. Specific bacterial species, such as *Porphyromonas gingivalis* and *Tannerella forsythensis*, have been shown to be important in the aetiology of periodontitis (3).

The inflammatory response may result in ulceration of the gingiva, which might allow the entry of bacterial cells, their products (including

lipopolysaccharides, or LPS; peptidoglycan fragments; and hydrolytic enzymes), or both into the systemic circulation (4). Research has demonstrated that the host response to periodontal infection results in the local production of cytokines and biological mediators such as prostaglandins and interleukins, as well as the systemic production of serum antibodies (5,6). Periodontitis leads to progressive and irreversible loss of bone and periodontal ligament attachment, as inflammation extends from the gingiva into adjacent bone and ligament. Signs and symptoms of progressing periodontitis include red, swollen gums that may appear to have pulled away from the teeth, persistent bad breath, pus between the teeth and gums, and loose or separating teeth (2).

Epidemiologic studies have identified a number of risk factors and risk indicators for periodontal attachment loss (PAL), including demographic,

socioeconomic, behavioural, genetic, and systemic factors (1,2).

Menopause has also been associated with destructive periodontal disease in older women (7,8). Peak ovarian function occurs before age 30 and then declines gradually. The menopause transition (climacteric, perimenopause), defined as the months and years surrounding the last menstrual period, is precipitated by fewer functioning follicles and ova, a consequent reduction in oestrogen level and an inability to respond to pituitary GnRH, FSH and LH. The initial sign of the transition, which may begin in the 40s, is a reduction in menstrual flow. This usually is followed by missed periods (9). Menopause is defined as the permanent cessation of menstruation due to loss of ovarian follicular function, and usually takes place between 45 and 55 years of age (10). Cigarette smoking is the only factor that has been consistently linked to earlier natural menopause. Julie reported that earlier onset of natural menopause among African American women is strongly associated with smoking and inversely associated with body mass index and oral contraceptive use (11,12,13). Oral contraceptives (14,15,16) low body mass index and low educational status (17) have also been associated with earlier menopause.

The physiological changes associated with menopause cause some women to experience uncomfortable symptoms. Postmenopausal women are at a higher risk of hypertension, pro-atherogenic lipid changes, diabetes, and severe cardiovascular disease, compared with their premenopausal counterparts (18). Multiple studies have demonstrated an association between postmenopausal status and increased levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), lipoprotein(a), and decreased levels of high-density lipoprotein-cholesterol (HDL-C) (19). Although premenopausal women are at a lower risk of heart disease than men, a twofold increase in risk of CVD follows menopause (20). Hot flushes have been recognized as a common menopausal symptom (21). This symptom is related to the central nervous system, or CNS. Oestrogen deficiency leads to dysregulation of the hypothalamic temperature control centre, resulting in vasomotor symptoms (9). Another symptom of menopause is night sweats. These vasomotor symptoms usually resolve spontaneously within two to four years of the last menses (22). Also, the postmenopausal period is associated with an increased risk of osteoporotic fractures, myocardial infarction, menstrual cycle disorders, vaginal dryness and possibly an early onset of Alzheimer's disease (23,24).

Osteoporosis is defined as a skeletal disorder characterised by low bone mass and

microarchitectural deterioration of bone tissue leading to enhanced bone fragility, with a consequent increase in fracture risk (25,26). The primary risk factors related to the development of osteoporosis include female sex and increasing age, but other risk factors have been identified: early menopause (younger than 45 years), cigarette smoking, high alcohol consumption, lack of physical activity, thin body frame, race (Asian or white), low calcium intake, excessive caffeine intake, certain medications (such as glucocorticoids and cytotoxic drugs) and certain diseases (27).

Osteoporosis is a major cause of morbidity, mortality and medical expense. It affects an estimated 75 million people in the United States, Europe and Japan combined, including one in three postmenopausal women and a majority of elderly people (28). Oestrogen deficiency is responsible for bone loss in postmenopausal women (29). However, hormone replacement of an adequate dosage can slow or prevent bone loss (30,31). Studies suggest that low oestrogen production after menopause is associated with increased production of interleukin 1 (IL-1), IL-6, IL-8, IL-10, tumour necrosis factor alpha, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor, which stimulates mature osteoclasts, modulates bone cell proliferation, and induces resorption of both skeletal and alveolar bone (32,33).

Burning mouth syndrome is characterized by a burning sensation on the tongue or at other oral sites, usually in the absence of clinical and laboratory findings. Affected patients often present with multiple oral complaints, including burning, dryness and taste alterations. Burning mouth complaints are reported more often in women, especially after menopause. Given in low dosages, benzodiazepines, tricyclic antidepressants or anticonvulsants may be effective in patients with burning mouth syndrome. Topical capsaicin has been used in some patients (34).

Sex Steroid Hormones

The homeostasis of the periodontium involves complex multifactorial relationships, in which the endocrine system plays an important role (35). Hormones are specific regulatory molecules that have potent effects on the major determinants of the development and integrity of the skeleton and oral cavity, including periodontal tissues (36). Hormones can be divided into four subgroups based upon their chemical structure: steroids, glycoproteins, polypeptides, and amines. Steroid sex hormones are derived from cholesterol and all have three rings of six carbon atoms each (37).

Oestrogen and progesterone are responsible for physiological changes in women at specific phases

of their life: puberty, menstrual cycle, pregnancy, menopause, and post menopause (38). Oestrogen, progesterone and chorionic gonadotropin (during pregnancy) all affect the microcirculatory system, 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 perivascular mast cells, increased vascular permeability, and vascular proliferation (39).

All natural androgens are derived from a 19-carbon tetracyclic hydrocarbon nucleus known as androstane. One of the most potent androgenic hormones, testosterone (17-hydroxy-androst-4-en-3-one), is synthesized by the Leydig's cells of the testes, the thecal cells of the ovary and the adrenal cortex. The biological activities of androgens can be observed in virtually every tissue of the body. The more important functions of androgens include: male sexual differentiation, development of adult male phenotype, facilitation of human sexual behaviour, and regulation of specific metabolic processes in the liver, kidneys, and salivary glands (35).

Androgens may play a significant role in the maintenance of bone mass (40) and inhibit osteoclastic function, inhibit prostaglandin synthesis and reduce interleukin-6 (IL-6) production during inflammation (41). Also, androgens enhance matrix synthesis by periodontal ligament fibroblasts and osteoblasts (42).

Sex steroid hormones exert considerable influence, both directly and indirectly, on cellular differentiation, proliferation, and growth in target tissues. In the oral cavity, androgens, oestrogens and progestins are known to affect several cell types. Sex steroid hormone research has focused primarily on two cell groups, the keratinocyte and the fibroblast (35). Oestrogen inhibits the expression of inflammatory cytokines important in bone resorption, and oestrogen deficiency may contribute to more intense gingival inflammation during periodontitis and subsequent oral bone loss, and may result in bone loss at both oral and skeletal sites. A number of studies have suggested that the risk of postmenopausal tooth loss is reduced by oestrogen replacement (43). Furthermore, lower oestrogen levels have been linked to gingival inflammation (44) and reduced clinical attachment levels (45).

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Menopause is also associated with significant adverse changes in the orofacial complex. Women appear to experience an increase in oral symptoms

that may result from endocrine disturbances (reduced estrogen), calcium and vitamin deficiency and various psychologic factors during their menopausal years (46,47). They may complain of dry mouth because of decreased salivary secretion, as well as a burning sensation of the mouth and tongue. Taste sensation may change, causing frequent complaints of a metallic taste (48). Also during menopause, women may experience dysesthesia, dental caries, periodontitis and an osteoporotic jawbone unsuitable for conventional dental devices and implants (9).

Some women develop concurrent senile atrophic gingivitis, in which an abnormal paleness of the gingival tissues develops. Other people develop a condition known as menopausal gingivostomatitis, which is characterised by gingivae that are dry and shiny, bleed easily and range in colour from abnormally pale to erythematous (9).

Peri- or post-menopausal women take hormone replacement therapy (HRT) to relieve climacteric symptoms and increase their quality of life (49,50). Hormone replacement in adequate dosage can slow or prevent bone loss (31). HRT includes oral administration, oestrogen containing dermal patches and tibolone (51). Marcos reported that the response to the HR therapy in periodontal disease is probably due to the existence of oestrogen receptors localized in the gingiva and the periodontal ligament (52). Some studies have suggested that postmenopausal women using HRT have increased tooth retention (53,54) and decreased periodontal destruction (7,55,56). Alex et al. found that postmenopausal HRT women had a two times greater likelihood of having periodontitis than premenopausal women. In contrast, postmenopausal HRT+ women did not have a greater chance of having periodontitis than premenopausal women. Although postmenopausal HRT- women showed significantly greater tooth loss than postmenopausal HRT+ women (57). Engeland et al. observed that premenopausal women aged 50 to 54 years healed similarly to women aged 18 to 43 years, whereas age-matched postmenopausal HRT- women showed delayed healing. The data indicated that HRT may improve mucosal wound healing in postmenopausal women (58).

Osteoporosis is more common in women than in men. Women are at a greater risk for osteoporosis after menopause (59) because oestrogen levels decline rapidly, which may lead to systemic bone loss (60). Bone turnover rate is higher in alveolar bone than long bones. Therefore, it was suggested that a systemic imbalance in bone resorption and deposition might be manifested earlier in the alveolar process than in other sites (1). Kribbs reported that postmenopausal women with osteoporosis had decreased mandibular bone

density, thinned cortex at the gonion, and more tooth loss than healthy postmenopausal women (61). The American Academy of Periodontology considers osteoporosis to be a risk factor for periodontal disease (62). A number of studies have investigated a possible relationship between periodontitis (63,64). Tezal et al. found that low bone mineral density was related to loss of interproximal alveolar bone (the alveolar bone between adjacent teeth) and, to a lesser extent, ligamentous attachment loss (64). Lundstrom et al. showed no significant differences in periodontal conditions or marginal bone levels of 70 year-old women with osteoporosis, as compared to those with a normal bone mineral density (65). Oestrogen deficiency caused a decrease in trabecular bone volume around the implants and a decrease in contact between the implant and the trabecular bone (9). Recent studies using animal models have examined the effects of a paucity of oestrogen on the initial osseointegration of dental implants. These studies showed that when new implants (without functional occlusion) are placed in previously ovariectomized animals, the trabecular bone volume around the implant and contact between the implant and new trabecular bone are markedly decreased in comparison with nonovariectomized animals (66,67).

Serum osteocalcin is presently considered a valid marker of bone turnover when resorption and formation are coupled and a specific marker of bone formation when formation and resorption are uncoupled (68). Bullon et al. reported that low serum osteocalcin concentration is associated with a significantly higher percentage of decrease in probing depth and clinical attachment level after periodontal treatment in postmenopausal women. Low saliva osteocalcin concentrations are significantly associated with a higher percentage of decrease in probing depth (69). Lorne et al. reported the therapeutic potential of long-term subantimicrobial-dose doxycycline therapy to reduce periodontal collagen breakdown and alveolar bone resorption in postmenopausal women (70).

Periodontal infections can increase the systemic release of inflammatory cytokines, which accelerate systemic bone resorption. Indeed, vitamin D deficiency has been associated with a cytokine profile that favours greater inflammation (e.g., higher levels of C-reactive protein and interleukin 6, and lower levels of interleukin 10), and vitamin D supplementation decreases circulating inflammatory markers. Therefore, Luca et al. suggest that menopausal women should maintain an adequate vitamin D status in order to prevent and treat osteoporosis-associated periodontal disease (71).

There is little knowledge of the prevalence of the periodontal microbiota among peri- and postmenopausal women (45). However, sex hormones

have long been considered to affect periodontal tissues and periodontal disease progression (72,73). Tarkila et al. reported that use of HRT did not correlate with periodontal health status, and led to lower numbers of samples positive for the periodontal pathogens *P. gingivalis* and *T. forsythia*. (74). Treatment of periodontal disease has been primarily directed towards a microbiological aetiology. Prevention of bone loss by modulating the host response to infection could be a new adjunctive method for the management of periodontitis (1). Bisphosphonates, the most commonly prescribed therapy for osteoporosis, inhibit systemic bone resorption (75).

Drugs that alter bone metabolism, such as oestrogen and bisphosphonate, were suggested by several case-control studies as a new approach to the treatment of periodontitis in postmenopausal patients (1).

This literature review highlights the importance of the effects of menopause on periodontal tissue.

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