Dynamics of periodontal tissue in menopause

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Abstract

Hormonal fluctuation orchestrates various gingival changes across the whole women's life cycle. In menopausal women, the periodontal disease, as interplay between periodontal pathogenic micro flora and host tissue, is also closely influenced by changes of hormonal flux. Desquamative gingivitis and higher incidence of reduced alveolar bone density are the main complaints. Though menopause osteoporosis and periodontal disease have many similarities, the relationship between these two chronic diseases and the effect of sex hormones decline on bone resorption is still inconclusive. A better clinical interplay between dentists and gynecologists would definitely result in improved periodontal health of menopausal women. Moreover, educational courses in both specialties, aiming to highlight this topic, might be important.

Keywords: *menopause, sex hormones, desquamative gingivitis, alveolar bone density*

Rezumat

Oscilațiile hormonale la femei dirijează de-a lungul vieții variate modificări gingivale. În menopauză, boala parodontală, ca rezultat al interacțiunii microflorei orale patogene cu țesuturile locale ale organismului-gazdă, este de asemenea strâns influențată de modificările hormonale. Principalele consecințe la nivelul cavității orale sunt gingivita descuamativă și reducerea densității osoase alveolare. Deși osteoporoza de menopauză și boala parodontală au multe similitudini, efectul reducerii secreției hormonale asupra resorbției osoase alveolare este neconcludent. O mai bună cooperare clinică între stomatolog și ginecolog ar ameliora statusul parodontal al femeilor la menopauză. Importante ar fi și cursurile postuniversitare în ambele specialități medicale axate pe acest subiect.

Cuvinte-cheie: *menopauză, hormoni sexuali, gingivită descuamativă, densitate osoasă alveolară*

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Dinamica țesuturilor periodontale în menopauză

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Introduction

Menopause is a period of woman's life characterized by permanent cessation of menstrual cycle that usually occurs between the ages of 45 and 55 years old. Though frequently the onset is installed naturally, sometimes may be prematurely observed as a result of radio- and chemotherapy targeted on ovaries or of their surgical removal by ovariectomy[1].

Hormonal fluctuations of estrogen and progesterone in women across their life cycle are mirroring in complex and various clinical changes of periodontal tissues[2,3]. In menopausal women, the periodontal disease, as interplay between periodontal pathogenic micro flora and host tissue, is also closely influenced in its onset and evolution by changes of hormonal flux[2-4].

Various mechanisms explain the role of female sex hormones in periodontal tissue physiology and pathology. By stimulating the collagen synthesis and angiogenesis, the estrogens may modulate the interaction of bacterial inflammatory mediators with local vascular response and connective tissue turnover[2]. The steroid hormones estrogen and progesterone, by targeting in periodontal tissue, their receptors are involved in gingival epithelium cytodifferentiation, collagen synthesis (estrogens) or in osteogenesis and alveolar bone resorption (progesterone)[3,4].

During menopause, especially in early climacteric, the hormonal level decline facilitates chronic canker sores due to mouth dryness and gingivostomatitis. Altered taste perception, burning mouth syndrome, atrophic glossitis, chronic desquamative gingivitis, and oral cancerophobia also occur[3,4].

However, in some perimenopausal and postmenopausal women, the oral discomfort is not directly related to sex hormones downregulation, but to subsequent added psychological disturbances. Moreover, in menopausal women, the oral discomfort is often associated with normal clinical appearance of oral mucosa[5].

Periodontal tissue – a target for steroid sex hormones

Numerous papers described the targeted cells in periodontium under the influence of sex hormones. All these cells from gingival epithelium, endothelium, periodontal connective tissue, immune system, tooth root cementum and bone become reactive while occur significant hormone fluctuation[4].

It is recognized that estrogens support epithelial keratinization and proliferation. In postmenopausal women, the downregulation of estrogens is responsible for reduced keratinization and downgrowth of epithelial attachment[4].

In cell cultures of gingival fibroblasts, progesterone inhibits protein synthesis, proliferation and IL-6 production, while estradiol stimulates proliferation, IL-6 and IL-8 release, and downregulates both collagen and non-collagen proteins[4].

Estrogen and progesterone are targeting the periodontal tissues alone or in conjunction with proinflammatory mediators from oral milieu. The effect of sex steroid hormones results mainly in improving the collagen turnover and angiogenesis stimulation, control of salivary peroxidases that exert an antibacterial action upon complex oral microflora, and initiating the autocrine or paracrine growth factors signaling pathways[2].

Sex steroid hormones receptors

Decades before, in periodontal tissues there were recognized receptors of female steroid hormones, estrogen and progesterone, both of them being physiologically involved in particular life phases of women[1,3,4].

Periodontal tissues have androgen, progesterone and two forms of distinct estrogen steroid hormones receptors, namely α-receptor and β-receptor[4]. In women, there were identified two kinds of estrogen receptors, estrogen receptor-α (ERα) and estrogen receptor-β (ERβ)[6].

One of these receptors, located among other tissues in cytoplasm of salivary glands and oral mucosa epithelial cells, is estrogen receptor-β[7,8]. ERβ was also found in epithelial cells of menopausal women in cases of desquamative gingivitis[9].

In fibroblasts of periodontal ligament, there were described both subtypes of estrogen receptors, α-receptor and β-receptor. Sometimes in gingival inflammation the expression of estradiol coupling receptors might be 10-fold elevated[4].

Once coupled to their specific receptors located in cell nucleus, the sex hormones induce gene activation and mRNA transcription. Subsequent to activation, the hormone is translocated to the nucleus and after binding to DNA it becomes a transcription regulator[1,10]. Independent on the genome, the sex hormones have also membrane effects, influencing neural transmission and calcium ions transfer[4].

While there was also located an androgen receptor for dihydrotestosterone, concerning the progesterone receptor the data are more evident in rabbit gingiva than in humans, though in fibroblasts there were proved nuclear specific receptors[4].

Sex hormones – inflammation interplay in menopause

The more evident clinical signs of gingival inflammation reported during periods of hormonal fluctuation rely upon the interplay of estrogen and progesterone with proinflammatory mediators[2,11].

Progesterone was mainly localized in basal and spinous epithelial layer, endothelial cells, pericytes and gingival fibroblasts. Its turnover is increased in gingival inflammation more significant in females than in males[12]. In periodontal inflammation, the progesterone-induced downregulation of IL-6 results in higher level of TNF-β and fibroblast metallo-proteinases activity, unlike the synthesis of acute phase proteins, which is reduced[2].

A positive correlation was also demonstrated between the degree of periodontal inflammation, gingival Δ4-5α-steroid hydrogenase and progesterone serum peak. On the day of ovulation, the exudates collected from gingival crevicular fluid reach a maximum level and their oscillation is more marked in case of already installed gingival inflammation[12].

Certain oral microorganisms, such as *Prevotella* spp., *Porphyromonas* spp. and *Treponema denticola*, can metabolize estrogens and progesterone. Though eventually the microbial turnover leads to these steroid hormones inactivation, their local concentration, even temporary, might have a harmful inflammatory outcome on periodontal tissue. Nevertheless, the ability of oral microflora to metabolize the sex steroid hormones depends on their presence in gingival crevice at the same range as serum concentrations, pH value, redox potential etc.[13]

The interplay of cytokines and proinflammatory mediators with steroid hormones in periodontal tissue is extremely intricate. The progesterone turnover orchestrated by *Treponema denticola* may result in triggering of gingival inflammation by two mechanisms, either by removing the PGE2 inhibiting effect on IL-1 secretion, or by progesterone-induced suppression of IL-1α and IL-1β release from monocytes[13].

Regarding the IL-17 family, which is known to participate in innate and adaptive immunity by proinflammatory and regulatory effects, it was observed that IL-17A and IL-17F were involved in mucosal defense against oral microflora. Both of them were identified in osteocytes of alveolar bone. IL-17A is predominant in healthy gingival epithelium, as compared to IL-17F which is mainly located in chorion. However, in periodontal inflammation, IL-17F prevails in both epithelial and subepithelial structures. In case of association between proinflammatory cytokine IL-1β and female sex hormone 17β-estradiol, the IL-17F expression is upregulated, proving one of the various interactions of cytokines and steroids in cells of periodontal tissue[14].

Chronic desquamative gingivitis

One of the outcomes clinically observed in estrogen downregulation is xerostomia, which in some cases worsens by association with antidepressant medications[15]. Subsequent to estrogen level drop in menopausal women, the whole oral mucosa including gingiva becomes drier, thinner and pale[1]. The macroscopic feature varies from clinical atrophic pale to zones of desquamative gingivitis and even leukoplakia[5].

Moreover, the simultaneous reduction of salivary secretion deteriorates the self-cleaning and facilitates superficial bacterial and fungal colonization which finally increases the risk of harmful agents penetration of gingival epithelium. Due to the reduced blood irrigation

and aggression of oral pathogens, the already affected gingiva is more prone to mechanical damage during mastication and tooth brushing and to delayed mucosal wound healing[1]. Mouth rinses with non- or low-alcohol concentration are recommended[15].

Microscopically, the thin gingival epithelium shows a nonspecific chronic inflammation and epithelial degeneration, illustrating an apparent disintegration of intercellular bridges, which results in cellular cohesion loss within the germinativum and spinosum cell layers. The keratin layer may be absent or present, but associated with parakeratosis. A breakdown of epithelial basement membrane might be also noted. The chronic inflammatory cells infiltration (lymphocytes, plasma cells, histiocytes) is diffusely spread in underlying connective tissue. Increased hyperemia and gingival edema are also depicted[16]. Someway the microscopic image is pretty similar to desquamative gingivitis associated to lesions of cicatricial pemphigoid[17].

While evaluating blood testosterone, estradiol and progesterone during gingival wound healing in women seem to occur in lower rates than in men. Commonly, progesterone promotes inflammation and estrogens have an antiinflammatory action, but in menopausal women prevails estrone, and not estradiol[18].

Accordingly, a difference was found in healing rate between younger or adult women and postmenopausal women, suggesting a deleterious effect of menopause. It was also noted that testosterone improves the mucosal healing by its involvement in angiogenesis and re-epithelization. Clinically, the gingival mucosa healing is similar in younger and aged non-menopausal women until the commencement of menopause[18].

While in post-menopausal women not taking hormone replacement treatment, a higher testosterone blood level accelerates the wound healing, it has to be taken into account that in those post-menopausal women under hormonal treatment the testosterone is downregulated, resulting in a prolonged healing of gingival wounds[18]. Noteworthy, in women under hormone replacement therapy, it was observed an obvious relief of painful oral symptoms[15].

Alveolar bone density in menopausal women

Bone is a living mineralized tissue undergoing across the life span of women a permanent process of remodeling. The main mechanisms that orchestrates its physical integrity are biomechanical strains and estrogens. In adult age, the highest bone density may be observed in molar area and the lowest under the bridge pontics where no chewing strain is developed, as compared to the bone situated around the abutment teeth[19].

The bone density is gradually increasing in female sex from puberty to adult age[20]. Later on, in old women, commonly the trabeculation is reduced, excepting those women who initially in their youth had a dense trabeculation. However, even in this case, the bone trabeculae are without doubt more delicate and less mineralized[19,21].

The bone loss occurs staidly, primary affecting for 4-8 years the trabecular bone in a rapid rate due to the onset of estrogen deficiency and secondary as a consequence of downregulated bone formation[15].

Subsequent to menopause – i.e. to estrogen secretion decrease –, a trabecular and cortical bone loss occurs. The predominant bone resorption comprises trabecular bone whose appearance becomes sparser as its surface is proportionally 10 times larger than that of compact one[19].

Though menopause osteoporosis and periodontal disease have many similarities, unfortunately the relationship between these chronic diseases and eventually the effect of sex hormones drop on bone resorption is still inconclusive since it is still difficult to establish the strength of additional bone remodeling effect induced in periodontal disease by bacterial proinflammatory cytokines[19,22-25].

Simultaneously with epithelial desquamation, in menopausal women also occurs a higher incidence of osteoporosis associated with lowering of bone density. Moreover, in early postmenopausal stage, the yearly rate of bone loss might be as high as 3-4%. Due to the calcium-phosphate imbalance, though the chemical composition is unchanged, the bone density decreases, resulting in unfavorable consequences of its strength[2,26].

In osteoporosis, the deficient osteoblasts fail to secrete bone matrix. The bones become slender and thinner since there prevails the resorption[27]. Though definitely osteoporosis is not the etiologic trigger of chronic periodontal disease, it was proved that it may negatively influence the evolution. It has to be highlighted that the lower jaw is more intensely affected by menopausal osteoporosis changes than the upper one[2]. On the other hand, it was revealed that extractions in complete denture wearers at 7-year period after total resorptive height loss in mandible is four times increased than in maxilla[28].

An experimental study on ovariectomized female albino mice revealed in periodontal membrane after 4-6 weeks more prominent blood vessels and a reduced number of thinner, more separated collagen fibers. Though there was observed bone formation, it was significant less evident as compared to controls[27].

Moreover, the diminution of appositional bone growth and density of collagen fibers in ovariectomized mice resembled the histological feature of 1-year-old healthy mice (at the age of physiologic cessation of sex hormones in female mice), explaining that the surgical removal of ovaries had a similar effect to physiologic changes in older healthy animals which mimicked menopause in humans[27].

It is of notoriety that the progression of periodontal disease may be evaluated by its association with various kinds of alveolar bone resorption[2,29]. On the other hand, the premenopausal and postmenopausal decline of female sex hormones also facilitates the alveolar bone resorption independently of periodontal inflammatory resorption[29]. Hormonal imbalance of menopausal women resulting in abrupt drop of circulating

estrogens, mainly estradiol, is playing a pivotal role of associated risk factor for bone resorption in already installed periodontal disease due the subsequent induction of bone loss and low bone mineral density (osteoporosis)[30].

Obviously, the bone turnover is governed by various and complex factors such as osteoprotegerin (OPG) – receptor of nuclear factor-kappa B ligand (RANKL) – receptor of nuclear factor-kappa B (RANK) system[31]. Actually, the alveolar bone resorption in menopausal women depends on multifaceted interaction of OPG-RANKL-RANK system with female sex hormones and proinflammatory cytokines[29].

Nevertheless, the possible link between periododontal bone loss and female sex hormones decline in menopausal women is still debated. Though it seems that the elevated level of serum OPG versus RANK in gingivitis might have a protective role against bone resorption, the differences related to normal health status of gingiva or to chronic marginal periodontitis in premenopausal/postmenopausal women found in gingival crevicular fluid are not statistically significant[29].

Conclusions

Hormonal fluctuation orchestrates various gingival changes across the whole women's life cycle. A better clinical interplay between dentists and gynecologists would definitely result in improved periodontal health of menopausal women. Moreover, educational courses in both specialties, aiming to highlight this topic, might be important. ■

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