

Review Paper

Influence of sex hormones on the periodontium

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Abstract

Objectives: Sex hormones have long been considered to play an influential role on periodontal tissues, bone turnover rate, wound healing and periodontal disease progression. The objectives of this review article are to (1) address the link between sex hormones and the periodontium, (2) analyse how these hormones influence the periodontium at different life times and (3) discuss the effects of hormone supplements/replacement on the periodontium.

Materials and Methods: Two autonomous searches were performed in English language utilizing Medline, Premedline and Pubmed as the online databases. Publications up to 2002 were selected and further reviewed. In addition, a manual search was also performed including specific related journals and books.

Results: It is certain that sexual hormones play a key role in periodontal disease progression and wound healing. More specifically, these effects seem to differentiate by gender as well as lifetime period. In addition, the influence of sex hormones can be minimized with good plaque control and with hormone replacement.

Conclusion: Despite profound research linking periodontal condition with sex hormones kinetics, more definitive molecular mechanisms and therapy still remain to be determined.

Key words: hormones; estrogen; periodontium; pregnancy; periodontal diseases

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Bacterial plaque has been established as the primary etiologic factor for the initiation of periodontal disease (Loe et al. 1965). However, it has also been shown that without a susceptible host the periodontal pathogens are necessary but not sufficient for disease to occur. Hence, the systemic factors/conditions of the host must be understood since they may affect disease prevalence, progression, and severity (Lang et al. 1983). Among these, sexual hormones have been suggested as important modifying factors that may influence the pathogenesis of periodontal diseases (Mariotti 1994, Parkar et al. 1998b, Hofbauer & Heufelder 2001).

Hormones are specific regulatory molecules that modulate reproduction, growth and development, maintenance of the internal environment, as well as

energy production, utilization, and storage (Mariotti 1994). Hormonal effects reflect physiological/pathological changes in almost all types of tissues of the body. Targets for a number of hormones such as androgens, estrogen, and progesterone have also been localized in periodontal tissues (Gornstein et al. 1999). Consequently, systemic endocrine imbalances may have an important impact in periodontal pathogenesis.

Researchers have shown that changes in periodontal conditions might be associated with variations in sex hormone levels. This association is evident in the recent periodontal disease classification (Armitage 1999), which includes the following hormone-related disease categories: puberty-associated gingivitis, menstrual cycle-associated gingivitis and pregnancy-associated gingivitis. There-

fore, the goal of this review paper is to discuss how sex hormones may influence the periodontium and periodontal wound/bone healing.

Steroid Sex Hormones

Because of their complexity and diversity, hormones are difficult to arrange into discrete groups, although they can be divided into four subgroups based upon their chemical structure – steroids, glycoproteins, polypeptides, and amines.

Steroid sex hormones are derived from cholesterol and as a common structure they have three rings of six carbon atoms. They are believed to play an important role in the maintenance of the skeletal integrity, including the alveolar bone. The steroid sex hormones such as estrogen and estradiol have been

known for their effect on bone mineral metabolism. Other bone turnover-related hormones include progesterone, testosterone and dihydrotestosterone, androstenedione, dihydroepiandrosterone, and sex hormone-binding globulin (Katz & Epstein 1993). Among these, estrogens, progesterone, and testosterone have been most linked with periodontal pathogenesis and therefore will be described in detail in the paper.

Estrogen and progesterone

Estrogen and progesterone are responsible for physiological changes in women at specific phases of their life, starting in puberty. Estrogen induces several of the pubertal developmental changes in females, and progesterone acts synergistically with estrogen to control the menstrual cycle and to inhibit follicle-stimulating hormone secretion by the anterior pituitary gland (Amar & Chung 1994). Both hormones are also known to promote protein anabolism and growth (Soory 2000a).

Both hormones have significant biological actions that can affect different organ systems including the oral cavity (Lundgren 1973a, b, Lundgren et al. 1973, Lopatin et al. 1980, Pack & Thomson 1980, Sooriyaamoorthy & Gower 1989a, Ojanotko-Harri et al. 1991, Mariotti 1994). Specifically, estrogens can influence the cytodifferentiation of stratified squamous epithelium as well as the synthesis and maintenance of fibrous collagen (Amar & Chung 1994). Estrogen receptors found in osteoblast-like cells provide a mechanism for the direct action on bone (Klinger & Sommer 1978, Aufdemorte & Sheridan 1981, Eriksen et al. 1988, Komm et al. 1988). These receptors were also located in periosteal fibroblasts, scattered fibroblasts of the lamina propria (Aufdemorte & Sheridan 1981), and periodontal ligament (PDL) fibroblasts (Nanba et al. 1989a), proving the direct action of sex hormones on different periodontal tissues.

Clinically, estrogen-sufficient patients have been reported to have more periodontal plaque without increased gingival inflammation when compared to patients with deficient levels of estrogens (Reinhardt et al. 1999). This suggests that inflammatory mediators may be affected by estrogen hormone level, which may be attributed to the production of prostaglandins (PGs) by the involvement of estradiol and progesterone. It is, therefore, speculated

that normal circulating estrogen levels might be essential for periodontal protection. In fact, the amount of circulating estradiol seems to be inversely correlated with the prevalence of periodontal disease (Placak et al. 1998). Other effects of the estrogens on the periodontium are listed in Table 1.

Progesterone is another sex hormone that has also been demonstrated to have direct effects on the periodontium (Table 2). Experimental, epidemiologic, and clinical data have demonstrated that progesterone is active in bone metabolism and may play an important role in the coupling of bone resorption and bone formation (Dequeker et al. 1977, Dequeker & De Muylder 1982, Lobo et al. 1984, Gallagher et al. 1991). Studies have shown that progesterone may exert its action directly on bone by engaging osteoblast receptors or indirectly by competing for a glucocorticoid receptor (Feldman et al. 1975, Chen et al. 1977).

Androgens (testosterone)

Androgens are hormones responsible for masculinization. Testosterone can be produced in the adrenal cortex, although the one from the testes is the most active form (Ganong 1997). Its secretion is regulated by ACTH and by pituitary adrenal androgen-stimulating hormone. The adrenal androgen androstenedione is converted to testosterone and to estrogens in the circulation and represents an important source of estrogens in men and in postmenopausal women.

Specific receptors for this hormone have been isolated in the periodontal tissues (Wilson & Gloyna 1970). Inter-

estingly, the number of receptors in fibroblasts tends to increase in inflamed or overgrown gingiva (Ojanotko et al. 1980). It is believed that an increasing matrix synthesis occurs on periodontal cells under testosterone influence (Ojanotko et al. 1980, Kasperk et al. 1989, Sooriyaamoorthy & Gower 1989a).

Testosterone has also been associated with bone metabolism, playing a role in the maintenance of bone mass (Morley 2000). A study performed on a group of men who were castrated for sexual offences showed that bone density suffered a rapid decrease that was sustained for a number of years after castration (Stepan et al. 1989). Kasperk et al. (1997) observed that both gonadal androgen dihydrotestosterone (DHT) and adrenal androgen dehydroepiandrosterone (DHEA) have a positive impact on bone metabolism, by stimulating bone cell proliferation and differentiation. A very effective way to analyze the effect of androgens on bone metabolism is the evaluation of the presence of biochemical markers of bone remodeling on bone tissue under the influence of those hormones. One of the bone remodeling markers that has been used for this objective is osteoprotegerin (OPG), which is a secreted decoy receptor that inhibits osteoclast formation and activation by neutralizing its cognate ligand (Kong et al. 1999, Teitelbaum 2000). This OPG action has been associated with a reduction in the loss of bone mineral density that is observed during periodontal disease progression (Kong et al. 1999). Szulc et al. (2001) found that serum concentrations of OPG increased significantly with age, and

Table 1. Effects of estrogen in the Periodontium

- increased amount of plaque with no increase of gingival inflammation (Reinhardt et al. 1999)
- inhibit proinflammatory cytokines release by human marrow cells (Gordon et al. 2001)
- reduce T-cell-mediated inflammation (Josefsson et al. 1992)
- suppress leukocyte production from the bone marrow (Josefsson et al. 1992, Cheleuitte et al. 1998)
- inhibit PMN chemotaxis (Ito et al. 1995)
- stimulate PMN phagocytosis (Hofmann et al. 1986)

Table 2. Effects of progesterone in the periodontium

- increase production of prostaglandins (self-limiting process) (ElAttar 1976b, Smith et al. 1986)
- increase polymorphonuclear leukocytes and PGE₂ in the GCF
- reduce glucocorticoid anti-inflammatory effect (Feldman et al. 1975, Chen et al. 1977)
- altered collagen and noncollagenous protein synthesis (Willershausen et al. 1991)
- alter PDL fibroblast metabolism (Nanba et al. 1989b, Sooriyaamoorthy & Gower 1989b, Tilakarante & Soory 1999a, b)
- increase vascular permeability (Abraham-Inpijn et al. 1996)

were positively correlated with free testosterone index and free estradiol index. They concluded that age as well as androgen and estrogen status are significant positive determinants, whereas parathyroid hormone (PTH) is a negative determinant of OPG serum levels in men (Szulc et al. 2001). These data suggest that OPG may be an important paracrine mediator of bone metabolism in elderly men and highlight the role of androgens in the homeostasis of the male skeleton.

Studies have also examined how the function of these hormones is controlled or regulated in the periodontium, looking specifically at the influence of different growth factors on the stimulation of DHT synthesis. Kasasa & Soory (1995) found significant stimulation of DHT synthesis by insulin-like growth factor (IGF) in gingiva and cultured fibroblasts. This finding suggests a possible mechanism of mediating inflammatory repair via the androgen metabolic pathway. The same authors later investigated the effects of interleukin-1 (IL-1) on the metabolism of androgens from chronically inflamed human gingival tissue (HGT) and PDL. In response to IL-1, HGT demonstrated a two-fold increase in DHT synthesis and a 3.5-fold increase in 4-androstenedione formation over control gingival tissue; the PDL showed a 9-fold increase in DHT synthesis in response to IL-1 and a 6-fold increase in 4-androstenedione formation over control ligament tissue. The observation of increased androgen metabolic capacity of PDL over HGT in response to IL-1 insult might be relevant to repair processes during inflammatory periodontal disease (Kasasa & Soory 1996).

Androgens also have a reciprocal effect on other important mediators of inflammation, more specifically on IL-6. This cytokine plays a major role in tissue damage during periodontal diseases, and is secreted by many cell types, including oral fibroblasts. In 1998, Parkar et al. investigated whether DHT affects the expression and regulation of IL-6 in gingival fibroblasts. Using ELISA, they observed that increasing DHT concentrations progressively reduced IL-6 production by gingival cells from both normal individuals and patients with gingival inflammation and gingival hyperplasia (Parkar et al. 1998a). Similar results were also reported by Gornstein et al. (1999). They found androgen receptors to be

Table 3. Effects of androgens in the periodontium

- stimulate matrix synthesis by osteoblasts and periodontal ligament fibroblasts (Ojanotko et al. 1980, Kasperk et al. 1989, Sooriyamoorthy & Gower 1989c)
- stimulate osteoblast proliferation and differentiation (Kasperk et al. 1997, Morley 2000)
- reduce IL-6 production during inflammation (Parkar et al. 1998b, Gornstein et al. 1999)
- inhibit prostaglandin secretion (ElAttar et al. 1982)
- Enhance OPG concentration (Szulc et al. 2001)

present in both human gingival and periodontal ligament fibroblasts, and reduced the production of IL-6 in the presence of androgens. It was suggested that elevated levels of androgens, more specifically testosterone and dihydrotestosterone, could affect the stromal cell response to an inflammatory challenge through downregulation of IL-6 production.

An *in vitro* study analyzed the relationship between various concentrations of male testosterone and the formation of radioactive PGs from arachidonic acid by gingival homogenate (ElAttar et al. 1982). They reported that testosterone had inhibitory effects in the cyclooxygenase pathway of arachidonic acid metabolism in the gingiva, and speculated that this sex hormone may have anti-inflammatory effects in the periodontium. These steroids can exert an anabolic effect on the tissues even when their anabolic capacity is decreased, as is the case during inflammation. These findings support the concept that androgens may have a limiting effect on periodontal inflammation during periodontal disease progression. From the research reported above, it can be concluded that the production of androgens is stimulated by the presence of proinflammatory cytokines commonly found on periodontally diseased tissues and is downregulated by proinflammatory cytokines concentration as well as the concentration of prostaglandins.

Table 3 lists the effects of androgens on the periodontium. Overall, androgens may protect the periodontium via a positive anabolic effect on periodontal cells, a negative effect on the production and presence of mediators of inflammation, and an inhibitory effect on osteoclastic function.

Factors Influencing Sex Hormone Effects on the Periodontium

Several factors may also influence how sex hormones affect the periodontium.

These include gender, age, and hormone supplements. These interactions will be thoroughly discussed in the following sections.

Gender

It is well understood that gender plays an important role in changes of the bone density throughout the entire skeleton. It is also known that women are much more affected than men (e.g. osteoporosis). Lau et al. (2001) reported that 80% of the osteoporotic patients are female, correlating with the higher frequency of hip fractures in females, who are also more likely to experience hormonal imbalance throughout their lives than males. In addition, when the influence of gender on periodontal disease was studied, females were considered for several years to be more affected than males (Marques et al. 2000, Novaes Jr & Novaes 2001), although contradicting data have been reported (Novaes Jr et al. 1996, Ship & Beck 1996, Albandar et al. 1999, Novaes Jr & Novaes 1999, Pihlstrom 2001, Yuan et al. 2001a, b). This disparity seems to be simply correlated with the fact that females are more likely to seek dental care than males (Hart et al. 1992, Novaes Jr & Novaes 2001). One observation that supports this notion is the presence of the same quantity and quality of subgingival bacteria, which is the most important risk factor for periodontal disease, in both men and women (Schenkein et al. 1993). Overall, the similarities/differences of periodontal pathogenesis among different sexes still requires much clarification. The role of the sex hormones in wound healing raises another question of how the endocrine system influences this disease, since sexual hormones differ with gender.

Regarding periodontal anatomic differences between genders, when the shape and height of the residual alveolar ridge were compared, it was found that the residual ridge in women is lower than that in men (Hirai et al. 1993). This

might be associated with the decreased amount of circulating estrogen found in women during menopause, since this condition is associated with a higher frequency of alveolar bone height loss, as well as decreased crestal and sub-crestal bone density (Payne et al. 1999). Those effects seem to be correlated with hormone concentrations and not to the increased susceptibility of the periodontal tissues, since it has been shown that males and females tend to have the same amount of receptors for sex hormones in periodontal tissues (Southren et al. 1978).

Age

The biological changes on the periodontal tissues during different time points such as puberty, the menstrual cycle, pregnancy, menopause, and oral contraceptive use have heightened interest in the relationship between steroid sex hormones and the health of the periodontium. Females seem to be more prone to hormone imbalance than males and therefore have been more extensively studied. It is important, however, to note that males also suffer from these variations (Morley 2000).

Puberty

Puberty is a complex process of sexual maturation resulting in an individual capable of reproduction (Ford & D'Occhio 1989, Halpern et al. 1998). It is also responsible for changes in physical appearance and behavior (Buchanan et al. 1992, Angold & Worthman 1993, Angold et al. 1999) that are related with increased levels of the steroid sex hormones, testosterone in males and estradiol in females.

During puberty, the production of sex hormones increases to a level that remains constant for the entire normal reproductive period. A peak prevalence of gingivitis was determined at 12 years, 10 months in females and 13 years, 7 months in males, which is consistent with the onset of puberty (Sutcliffe 1972). Changes in hormone levels have been related with an increased prevalence of gingivitis followed by remission (Massler et al. 1950, Curilovic et al. 1958, Sutcliffe 1972, Daniell 1983), a situation that is not necessarily associated with an increase in the amount of dental plaque (Sutcliffe 1972).

Table 4. Clinical and microbiologic changes in the periodontium

During puberty

- enhanced blood circulation in the end terminal capillary loops and associated increased prevalence of gingivitis/bleeding tendency (Muhlemann 1948, Massler et al. 1950, Curilovic et al. 1958, Sutcliffe 1972, Daniell 1983)
- higher bacterial counts (especially *Prevotella intermedia* (*Pi*) and *Capnocytophaga* species) (Kornman & Loesche 1982, Mombelli et al. 1990, Mariotti 1994)

During pregnancy

- increased tendency for gingivitis and larger gingival probing depths (Loe & Silness 1963, Silness & Loe 1964, Miyazaki et al. 1991, Robinson & Amar 1992, Machuca et al. 1999, Soory 2000a) and periodontitis (Robinson & Amar 1992)
- increased susceptibility to infection (Cohen et al. 1969, Brabin 1985)
- decreased neutrophil chemotaxis and depressed antibody production (Sooriyamoorthy & Gower 1989b, Raber-Durlacher et al. 1991, Raber-Durlacher et al. 1993)
- increased numbers of periodontopathogens (especially *Porphyromonas gingivalis* and *Pi*) (Kornman & Loesche 1980, Tsai & Chen 1995)
- increased synthesis of PGE₂ (ElAttar 1976b)

Table 5. Effect of osteoporosis upon periodontium

- Poor wound healing: less attachment formation (von Wöwern et al. 1994)
- Reduced bone mineral content in the jaws (von Wöwern et al. 1994, Payne et al. 1999)
- Increase of periodontitis and tooth loss (Mittermayer et al. 1998)

The subgingival microflora is also altered during this period since the bacterial counts increase in number, and there is a prevalence of certain bacterial species such as *Prevotella intermedia* (*Pi*) and *Capnocytophaga* species (Yanover & Ellen 1986, Gusberty et al. 1990). *Pi* has been shown to possess the ability to substitute estrogen and progesterone for menadione (vitamin K) as an essential growth factor (Kornman & Loesche 1982). This may explain the association between increased estrogen concentrations and the elevated counts of *Pi*. On the other hand, *Capnocytophaga* species, which often increase during puberty, have been associated with the increased bleeding tendency observed during this period of time (Gusberty et al. 1990). Mombelli et al. (1990) evaluated longitudinal changes, during a period of 4 years, in the composition of the subgingival microbiota of children between 11 and 14 years of age. They observed that children who developed marked and sustained puberty gingivitis had higher frequencies of spirochetes, *Capnocytophaga* sp., *Actinomyces viscosus*, and *Eikenella corrodens* than the children without puberty gingivitis. They also noted that a resurgence of *Pi* was correlated with a high bleeding tendency in these patients.

The data strongly indicate that with the influence of sex hormones, children in puberty experience an exaggerated gingival inflammatory response to pla-

que. Table 4 lists the clinical and microbiological changes observed in the periodontium during puberty.

Menstrual cycle

The menstrual cycle is controlled by the secretion of sex hormones over a 25–30-day period and is responsible for continued ovulation until menopause (Ganong 1997, McCartney et al. 2002). In humans, the menstrual cycle can be divided into two phases: a follicular or proliferative phase, and a luteal or secretory phase. During the first phase, there is an increase in estrogen levels. At the same time, the luteinizing hormone stimulates progesterone secretion and ovulation. After ovulation, the luteal phase is characterized by an increase in progesterone and estrogen secretion. At the end of this phase, and if fertilization has not occurred, the plasma levels of progesterone and estradiol decline because of the demise of the corpus luteum (Laufer et al. 1982).

Generally, the periodontium does not exhibit evident changes during the menstrual cycle. Nonetheless, two different clinical findings have been observed in the oral cavity: gingival bleeding and increased production of gingival exudate (Kribbs & Chesnut 1984, Kribbs et al. 1989, Kribbs 1990, 1992, Grodstein et al. 1996a, b). In addition, ulcerations of the oral mucosa and vesicular lesions have also been

noted (Segal et al. 1974) in the luteal phase of the menstrual cycle, although the incidence is low (Segal et al. 1974, Ferguson et al. 1978, 1984). However, the specific mechanism of how steroid sex hormones influence vesicle/ulceration formation remains to be determined (Mariotti 1994).

Pregnancy

Some of the most remarkable endocrine alterations accompany pregnancy. During this period, both progesterone and estrogen are elevated due to continuous production of these hormones by the corpus luteum. By the end of the third trimester, progesterone and estrogen reach peak plasma levels of 100 and 6 ng/ml, respectively, which represent 10 and 30 times the levels observed during the menstrual cycle (Zachariassen 1989, Amar & Chung 1994, Mariotti 1994).

Susceptibility to infections (e.g. periodontal infection) increases during early gestation due to alterations in the immune system (Cohen et al. 1969, Brabin 1985) and can be explained by the hormonal changes observed during pregnancy (Hansen 1998, Smith 1999), suppression on T-cell activity (Priddy 1997, Taylor et al. 2002), decreased neutrophil chemotaxis and phagocytosis, altered lymphocyte response and depressed antibody production (Sooriyamoorthy & Gower 1989a, Raber-Durlacher et al. 1991, 1993, Zachariassen 1993), chronic maternal stress (Culhane et al. 2001), and even nutritional deficiency associated with increased nutritional demand by both the mother and the fetus (Wellinghausen 2001). Consequently, increased susceptibility for certain infections such as *Helicobacter pylori* (Lanciers et al. 1999), *Coxiella burnetii*, *Listeria monocytogenes*, *Toxoplasma gondii* (Smith 1999), and virus infections (e.g. hepatitis E virus, rubella, herpes, and human papilloma virus) has also been observed and reported (Priddy 1997).

These immunologic changes might also be responsible for periodontal pathologic conditions observed during pregnancy such as pregnancy gingivitis (Loe & Silness 1963, Silness & Loe 1964, Miyazaki et al. 1991, diLauro & Tarturo 1971, Machuca et al. 1999, Soory 2000a), pregnancy granuloma, periodontitis, and dental caries (diLauro & Tarturo 1971). The increased synthesis of PGE₂ observed when estradiol

and progesterone are present in higher concentrations, such as occurs during pregnancy (ElAttar 1976a), may also contribute to these pathologic changes (Offenbacher et al. 1984, 1986). On the other hand, periodontal pathogens such as *Pi* and *Porphyromonas gingivalis* (*Pg*) can also use female sex hormones such as progesterone or estradiol as a source of nutrients. These bacteria are generally increased in the gingival crevicular fluid of pregnant women, a situation that is positively correlated with the severity of pregnancy gingivitis (Kornman & Loesche 1980, Tsai & Chen 1995). These microbiological shifts usually do not last postpartum (Raber-Durlacher et al. 1994). Nonetheless, (Jonsson et al. 1988) found that *Pi* remains consistent even after the end of the pregnancy.

Aside from the transient increases in bleeding (Arafat 1974, Miyazaki et al. 1991), gingivitis, larger gingival probing depths (Hugoson 1971, Miyazaki et al. 1991), increased gingival crevicular fluid flow (Hugoson 1971), and the subgingival microbial shift, pregnant women in good health are unlikely to experience any significant gingival responses that would have serious clinical implications (Amar & Chung 1994).

Menopause and postmenopause

In the premenopausal women, the principal circulating estrogen is 17 β -estradiol (Katz & Epstein 1993). As women approach menopause, the levels of estrogen begin to drop mainly during the late follicular and luteal phase of the menstrual cycle (Sherman & Korenman 1975). As a result of this physiologic situation, irregular cycles start to occur. Frequently, the time frame between regular cycles and the cessation of menstrual periods, called *perimenopausal transition*, is 2–7 years (Treloar et al. 1970). During this period, the concentration of circulating estrogen decreases while follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations increase (Monroe & Menon 1977). Consequently, the effects of estrogen listed in Table 1 are reduced, therefore compromising the anti-inflammatory effect of this hormone on the periodontium.

Progesterone is another sex hormone that may play an important role in bone metabolism during pre- and postmenopause (Katz & Epstein 1993). It is believed that ovarian deficiency and

associated alterations, but not aging, are the predominant causes of bone loss during the first two decades after menopause (Richelson et al. 1984). Researches have shown that progesterone may compete with glucocorticoids for an osteoblast receptor and inhibit the glucocorticoid-induced osteoporosis. Therefore, postmenopausal bone density reduction may be the result of a combination of the inhibition of osteoclast downregulation by reduced estrogen and the increased cortisol inhibition of osteoblasts via the reduction of competition with progesterone (Katz & Epstein 1993).

Menopause also affects the concentration of circulating androgens. Before menopause, 50% of the circulating androstenedione is derived from the ovaries and 50% from the adrenals. With the ovarian failure that typically occurs with menopause, the concentration of circulating androgens is reduced by about 50% (Judd 1976). It has been suggested that the peripheral conversion of androgens to estrogens may be the main factor for protecting bone (Katz & Epstein 1993), since, as previously mentioned, estrogens have an inhibitory effect on osteoclastic action. Testosterone was also found to be positively correlated with bone density, a finding that is supported by the evidence of low concentrations in osteoporotic patients (Davidson et al. 1982, Steinberg et al. 1989).

A number of studies have linked menopause with some periodontal conditions, although the different methods applied to assess osteoporosis, alveolar bone loss, and periodontitis make that literature difficult to analyze. As suggested, osteoporosis is responsible for less crestal alveolar per unit volume, a condition that may promote quicker bone loss when encountered with infections such as periodontal infections (Wactawski-Wende et al. 1996).

It has been reported that the incidence of periodontitis correlates with signs of generalized osteoporosis, and lower bone density of the mandible with an increased incidence of periodontal disease (Groen et al. 1968, Klemetti et al. 1994, Krall et al. 1994, Krall 2001, Wactawski-Wende 2001), although other studies do not show consistent relationships between those aspects (Kribbs 1990, Elders et al. 1992). Reinhardt et al. (1999) reported that patients with estrogen deficiency showed more bleeding on probing

(BOP) and a higher frequency of ≥ 2 mm of clinical attachment loss than patients without estrogen deficiency. They then speculated that estrogen supplementation is important in reducing gingival inflammation and limiting the frequency of clinical attachment loss in osteopenic/osteoporotic women in early menopause. However, when Wingrove et al. (1979) compared gingival biopsies taken from postmenopausal females and from younger women with regular menses, no significant differences in the gingival tissues associated with changes in the levels of sex hormones were found.

The same correlation between estrogen deficiency, osteopenia/osteoporosis, and the prevalence of tooth loss was also reported (Daniell 1983, Kribbs et al. 1989, Elders et al. 1992, von Wörm et al. 1994, Paganini-Hill 1995a, Grodstein et al. 1996a, Mittermayer et al. 1998, Reinhardt et al. 1999). An important idea that should be kept in mind is that in many of these cases, tooth loss might be influenced by factors other than periodontal disease.

The severity of osteoporosis was found to be statistically significantly associated with the height of the residual alveolar ridge (Hirai et al. 1993). Payne et al. (1999) in a 2-year longitudinal study examined alveolar bone height and density changes in osteoporotic/osteopenic women compared with women with normal lumbar spine bone mineral density (BMD). In total, 38 postmenopausal women with a past history of periodontal disease on a 3- or 4-month periodontal maintenance interval were monitored; 21 had normal bone mineral density and 17 had diagnosed osteoporosis. Results from this study indicated that osteoporotic/osteopenic women exhibited a higher frequency of alveolar bone height loss, as well as crestal and subcrestal density loss when compared to women with normal bone density. This corresponds to the decreased amount of circulating estrogen present in the osteoporotic/osteopenic women.

Even though osteoporosis has been considered a risk for periodontal disease (Page & Beck 1997, Krejci & Bissada 2000, Pihlstrom 2001), many authors still question if the associations reported above are just concomitant findings or if osteoporotic patients have an increased susceptibility to periodontal disease, which would explain the increased incidence of edentulous patients and

more severe forms of periodontal disease. In 1997, Streckfus et al. studied the relationship among alveolar bone loss, alveolar bone density, second metacarpal density, salivary and gingival crevicular fluid IL-6, and IL-8 concentrations in premenopausal and postmenopausal healthy women receiving estrogen therapy. Other than observing that postmenopausal women on estrogen therapy had more alveolar bone loss, more missing teeth, and reduced alveolar and second metacarpal bone density than premenopausal women, the authors also noticed that postmenopausal women on estrogen therapy had higher salivary IL-6 concentrations than premenopausal women. From this study it was concluded that levels of bone resorptive cytokines in saliva may be secondary to changes in menopausal status, and that these changes may predispose loss of alveolar bone with resultant loss of teeth (Streckfus et al. 1997).

Although research shows a linkage between menopause and increased signs of periodontal disease and a reduction in alveolar bone height, it is important to note that both menopausal and postmenopausal women who are in good gingival health should not be considered to be at an increased risk of periodontal disease, although these physiologic conditions may affect the severity of the present disease (Amar & Chung 1994).

Hormone replacement

As addressed above, females experience hormonal changes under both physiological (e.g. menstrual cycle, pregnancy) and nonphysiological conditions (e.g. hormone therapy, use of oral contraceptives). The effects of these treatments on the periodontium have been a center of focus for understanding the interaction between sex hormones and periodontium health (Soory 2000b).

Contraceptives

Hormonal contraceptives induce a hormonal condition that stimulates a state of pregnancy to prevent ovulation by the use of gestational hormones. Oral contraceptive agents are one of the most commonly used classes of drugs. The most commonly used contraceptives nowadays consist of low doses of estrogens (30 $\mu\text{g/day}$) and/or Progestins (1.5 mg/day) (Chihal et al. 1975, Brown et al. 2001, 2002).

The influence of contraceptives on the periodontium is not limited to increases in inflammation and in the amount of gingival exudates (Lindhe & Bjorn 1967, Lynn 1967, Groen et al. 1968, el-Ashiry et al. 1971, Knight & Wade 1974, Pankhurst et al. 1981). These drugs have also been associated with an increase in the prevalence of dry socket after dental extraction (Catellani 1979), and accelerated progression of periodontal disease (higher gingival index scores and more loss of attachment) when they are used long-term. In contrast, some authors have found no significant influences on the periodontal clinical parameters when comparing oral contraceptives to non-medicated control groups (Moshchil et al. 1991).

Hormone replacement therapy in postmenopausal women

Osteoporosis, which is defined as a systemic condition characterized by a decrease in the bone mineral density of at least 2.5 times the normal values in a healthy young female, is a major health problem in postmenopausal women. In Western societies, more than one-third of the female population above the age of 65 years suffers from signs and symptoms of osteoporosis, a disorder characterized by low bone mass. Estrogen deficiency is the dominant pathogenic factor for osteoporosis in women (Reinhardt et al. 1999). Although hormonal replacement in an adequate dosage can slow or prevent bone loss (Ettinger 1993, Allen et al. 2000), only a small percentage of postmenopausal women receive such therapy, and many who do fail to comply with the prescribed regimen because of the fear of cancer, irregular bleeding, and other minor side effects (Bjorn & Backstrom 1999, Bai et al. 2000, Kenemans et al. 2001, Schneider 2001).

Progesterone alone is not effective in preventing postmenopausal bone and tooth loss (Ettinger 1988, Jeffcoat 1998), but when combined with estrogen it is believed to uncouple formation and resorption to diminish bone resorption induced by estrogen (Christiansen et al. 1985).

Paganini-Hill (1995a) analyzed the effects of estrogen replacement therapy (ERT) on the prevention of tooth loss and the need for dentures in older women. Results from this study indicated that the proportion of edentulous

women decreased with increasing duration of ERT. The author therefore concluded that ERT may be beneficial in preventing tooth loss and the need for dentures in older women

Reinhardt et al. (1999) analyzed prospectively the influence of serum estradiol (E_2) levels and osteopenia/osteoporosis on common clinical measurements of periodontal disease over a 2-year period. E_2 status, which was conditioned by the presence of ERT, did not influence the percentage of sites losing clinical attachment level for either periodontitis or nonperiodontitis groups, but when nonsmoking osteopenic/osteoporotic periodontitis patients were evaluated, E_2 -deficient subjects had more BOP and a trend toward a higher frequency of ≥ 2.0 mm clinical attachment loss than E_2 -sufficient subjects. These data suggest that E_2 supplementation (serum $E_2 > 40$ pg/ml) is associated with reduced gingival inflammation and a reduced frequency of clinical attachment loss in osteopenic/osteoporotic women in early menopause.

Other than just having a positive effect on the alveolar and skeletal bone density, hormonal replacement therapy may have other positive effects such as reduction of the risk of fatal and nonfatal myocardial infarction, ischemic heart disease, and stroke by 20–40%, and even a reduction in the prevalence of Alzheimer's disease (Paganini-Hill 1995b, c).

The available data indicate that hormone replacement therapy should be suggested for women during menopause since several pathologic conditions common during this period of time can be avoided or at least reduced in severity.

Influence of Sex Hormones on Periodontal/Implant Wound Healing

The effects of sex hormones in the wound healing of different organs have been studied and, in some cases, proved. Even though the direct effect of these hormones in periodontal wound healing is still far from being completely studied and clarified, other systems like the brain (Chowen et al. 2000) and the ligaments (Frank et al. 1999) are already known to be targets for sex hormones during the wound healing processes. At a molecular level, research has also shown that sex hormones have a regulatory effect on growth factors involved in the wound healing such as the keratinocyte growth factor (Rubin et al. 1995), which has

been known to have wound healing regulatory effect including stimulation of proliferation, migration, and morphogenesis of pluripotential cells.

However, the influence of sex hormones on periodontal wound healing is still largely unknown. As discussed above, people with hormone deficiencies may show more periodontal disease/destruction. However, the mechanisms of how this occurs remain to be determined. Overall, lack of sex hormones often causes the reduction of bone density (Reinhardt et al. 1999). Therefore, some authors consider the osteoporotic status a risk factor for implant success (Roberts et al. 1992) and others disagree. For example, Cuenin et al. studied the association between sex hormone levels and dental implant success in three patient groups: (1) male controls, (2) females with high estrogen, and (3) females with low estrogen. They found that the balance of alveolar osseous wound healing was not influenced by temporal fluctuations of the ovulatory cycle (Cuenin et al. 1997).

More research is definitely needed to improve the understanding of how sex hormones influence the overall periodontal and implant wound healing.

Conclusion

Sexual hormones play an important role in influencing periodontal disease progression and wound healing. These effects are different depending on the gender as well as the lifetime period analyzed. It is also clear that not all patients and their periodontium respond in the same way to similar amounts of circulating sexual hormones.

In addition, the influence of sex hormones can be minimized with good plaque control as well as with hormone replacement therapies; however, the true mechanism of how these interactions actually occur remains to be determined.

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Zusammenfassung

Einfluss von Sexualhormonen auf das Parodontium

Männliche und weibliche Sexualhormone wurden schon lange einen wichtigen Einfluss auf das parodontale Gewebe, die Knochenumsatzrate, die Wundheilung und die parodontale Erkrankungsprogression ausübend betrachtet. Der Einfluss dieser Hormone auf das Parodontium unterscheidet sich zu verschiedenen physiologischen Phasen (z.B. Pubertät, Schwangerschaft, post Menopause) und mit der Einnahme von Pharmaka (z.B. Antikonzepativa, Hormonsubstitution). Deshalb ist der Zweck dieses Reviewartikels (1) die Beziehung zwischen Sexualhormonen und dem Parodontium zu beschreiben, (2) die Analyse des Einflusses dieser Hormone auf das Parodontium zu unterschiedlichen Lebenszeiten und (3) die Effekte von Hormonunterstützung/substitution auf das Parodontium zu diskutieren.

Résumé

Influence des hormones sexuelles sur le parodonte

On a longtemps considéré que les hormones sexuelles, aussi bien masculines que féminines, jouaient un rôle important sur les tissus parodontaux, le taux de remaniement osseux, la cicatrisation et la progression de la maladie parodontale. L'influence de ces hormones sur le parodonte est différente en fonction des divers conditions physiologiques (par exemple, la puberté, la grossesse, et après la ménopause) et les prises de médicaments (par exemple, la pillule contraceptive et les traitements hormonaux de substitution). Aussi, cette revue critique de la littérature se propose (1) de faire le point sur les liens entre les hormones sexuelles et le parodonte (2) d'analyser la façon dont ces hormones influencent le parodonte lors des différentes étapes de la vie, et (3) discuter les effets des hormones de substitution sur le parodonte.

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