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Effects of Menopause on the Oral Cavity

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Abstract

The influence of female hormones on periodontal tissue is well documented for a number of conditions, such as puberty and pregnancy...Low oestrogen levels following the decrease or cessation of ovarian function may also, to show relationship between menopause and periodontal disease. The menopause is one period during which various symptoms will be declared. Some can relate to the oral cavity, they are mainly the symptoms of oral discomfort, gingivitis and periodontitis.

Subject Areas

Dentistry

Keywords

Cytokines, Menopause, Osteoporosis, Periodontitis

1. Introduction

Menopause is not an illness, even if it does mark the end of a woman's fertile period. But it is a biological transformation (like puberty) between sexual maturity and aging. It's the transition period a woman must go through before entering a period of life that is said to be one of the most serene of the various ages of existence.

During this period, hormonal changes bring about organic and psychic changes that manifest themselves in various symptoms (hot flashes, insomnia, irritability, dry mucous membranes, osteoporosis...).

Some of these symptoms are particularly noticeable in the oral cavity: dryness and burning sensations in the oral mucosa (oral discomfort syndrome), gingivitis

and periodontitis in the bone, which can be aggravated by systemic osteoporosis.

2. General Information on the Menopause

2.1. Sex Hormones

The main sex hormones in women are estrogen and progesterone. These are lipids synthesized in the cytosol from cholesterol and are called steroid hormones [1]. They are secreted by the ovaries and placenta (progesterone) during the reproductive period, under the influence of two hormones: (STEVENS) [2].

- FSH (follicle-stimulating hormone).
- LH (luteinizing hormone).

2.2. Definition and Physiology of Menopause

2.2.1. Definitions

Menopause is defined as a permanent cessation of menstruation resulting from a loss of ovarian follicular activity.

The etymological origin of menopause is two Greek words: men, menos: months= menstruation and pausis= cessation, meaning "cessation of menstruation".

Menopause is a physiological phenomenon that begins after the last menstrual period, after which there will be no more menstruation and therefore no ovulation [3].

For the menopause to be declared, there must be a period of one year without menstruation. This event occurs at a variable age, but generally between 45 and 52.

Menopause is considered the final stage in a complex process involving the female genital tract and endocrine system and is characterized by the cessation of production of the sex hormones estrogen and progesterone.

2.2.2. Physiology of the Menopause

The average woman reaches menopause between the ages of 45 and 52 [4].

Estrogen secretion is maintained, but progesterone secretion declines, so during the menopausal transition, women are exposed to appreciable concentrations of circulating estradiol (up to 500 pg/ml) (MAUVIS JAWIS and SITRUK WAVE 1986) [5].

After a year without menstruation, the woman is menopausal and the endocrine and exocrine functions of the ovaries are abolished.

At post-menopause, estradiol levels fall by 80%, estrone by 20% and progesterone by 85% [6]. Estrone is the main post-menopausal estrogen, derived from the conversion of androstenedione in adipose tissue, but is much less active than estradiol.

In the pre-menopause, estradiol concentrations range from 50 to 100 pg/ml and in the post-menopause from 5 to 25 pg/ml, while progesterone concentrations range from 0.5 to 20 mg/ml in the pre-menopause and 0.5 mg/ml in the post-menopause [7].

2.3. Stages of Menopause and Their Hormonal Changes

Before menstruation ceases or menopause sets in, women go through several stages: peri-menopause, menopause and post-menopause or confirmed menopause [3] [4].

2.3.1. Premenopausal Period

According to the World Health Organization, 'it is the period in which clinical and/or biological signs appear that indicate the approach of menopause, and it lasts for at least one year after the last menstrual cycle [3].

This results in a hormonal imbalance between the secretion of oestrogen and progesterone. Oestrogen secretion continues while progesterone secretion decreases.

Cycles become longer or shorter. FSH levels rise during the cycle, leading to increased stimulation of the follicles, and therefore oestradiol secretion is often excessive [5].

2.3.2. Menopause

The date of menopause is the date of the last menstrual cycle, and can only be determined retrospectively.

In fact, to confirm that menopause is final, a period of time must pass without the return of the menstrual cycle, by definition, this period is set at one year [3] [8].

This period leads to complete hormonal deficiency. We note the continued presence of primary follicles, but they become less sensitive to stimulation by FSH and LH. 17β estradiol gradually decreases.

2.3.3. Post-Menopause

This is the period in which the consequences of hormonal deficiency become apparent, as ovarian secretion stops, but androgen secretion continues, which also stops over time.

After menopause, the ovaries do not contain follicles, and their secretion of steroids almost completely stops. Through negative feedback, the rate of gonadal hormone secretion increases significantly (bad) [5].

Estrogen is the main hormone after menopause, and it comes mainly from the conversion of androstenedione by aromatase in adipose tissue [9].

Consequently, in the postmenopausal phase, oestrogen production decreases significantly, while androgen production decreases.

The level of oestradiol decreases by 80%, the level of oestrogen by 20%, and the level of progesterone by 85%.

Adipose tissue is the main source of oestrogen production after menopause.

FSH levels increase 10 to 20 times, while LH levels increase 3 times during the first years after menopause, then gradually decrease.

As this transitional phase progresses towards confirmed menopause, hormonal changes will affect many organs [10]:

- The vagina: It becomes narrower, drier, less elastic, and more susceptible to infection.
- The urinary tract: It becomes susceptible to urinary tract infections with pain during urination. Women in menopause may also complain of urinary incontinence (not specific to menopause).
- Mind: It has long been believed that menopause exposes women to depression and sadness, but recent large-scale epidemiological studies have shown that menopause is a protective factor. This does not negate the validity of other studies that have shown that early menopause makes women more prone to anxiety and depression.
- Cardiovascular system: Oestrogen reduces the risk of heart disease and stroke in women compared to men exposed to the same risks. However, after menopause, the risk of these diseases increases, as does the level of fat in the blood, which determines the level of cholesterol (LDL and HDL).
- Bones: With a decrease in oestrogen, bones become thin and brittle and more prone to fractures, leading to osteoporosis.
- It has also been proven that the gums and bones in the jaw can be affected by these hormones and are susceptible to disease [11].

2.4. Oral Manifestations of Menopause

There are three types:

- Oral discomfort.
- Gingivitis.
- Periodontitis.

2.4.1. Oral Discomfort

The symptoms often described by women at the onset of menopause are: a feeling of dry mouth (related to hyposialia), burning pain, altered taste perception, and difficulty swallowing or speaking.

These complaints are found in 20% to 90% of menopausal women [9] [12].

According to ZACHARIASEN [9], 46% of post-menopausal women experience this discomfort, compared to 6% of pre-menopausal women.

The causes of these symptoms are [13]:

- Geriatric (ageing).
- Psychological and psychosomatic.
- Hormonal.

1) Burning sensations or burning mouth syndrome (BMS) [14] [15]

BMS is a chronic syndrome of the face that is not accompanied by lesions in the mucosa, regardless of the intensity of the pain [14].

These sensations may be located in the gums (gingivodynia) and/or tongue (glossodynia) and may also be accompanied by dysgeusia (altered taste).

The different aetiologies of burning sensations are grouped into three categories [15]:

Local, systemic, and psychological.

♣ Local factors associated with BMS are:

- Mechanical irritation in the case of dentures.
- Poor oral health.
- Presence of erosion and/or ulceration.
- Mucosal atrophy.
- Gingivitis.
- Periodontitis.
- Allergic reaction to methyl methacrylate monomer, nickel, mercury and cobalt.
- Allergic reaction to certain foods.
- Dysfunctions or parafunctions.
- The quantity and/or quality of saliva, which can be altered by radiation, medication (antidepressants, antihypertensives, etc.) or systemic diseases.

♣ Systemic factors:

- Anemia.
- Deficiencies in vitamins B12, B2, B1, B6 and folic acid.
- Diabetes.
- HIV infections.
- Immunological disorders.

♣ Psychological factors:

- Anxiety.
- Depression.
- Psychological processes.
- Cancerophobia.

Depression is noted as the most common aetiological factor.

2) Dry mouth

Also known as xerostomia, this condition is caused by a quantitative or qualitative deficiency in saliva secretion. It is a common syndrome that is often overlooked.

When it occurs, the cause must be identified so that it can be treated and oral complications prevented [16] [17].

Xerostomia has multiple causes. The most common factor is the use of medications with anticholinergic effects.

Systemic conditions such as diabetes and connective tissue diseases are also involved in xerostomia.

Finally, stress can cause a decrease in saliva production.

This feeling of dryness can cause burning pain.

Suggestive signs:

- Sticky lips
- Lack of saliva retention under the tongue.
- The tongue sticks to the inside of the cheeks.

- Enlarged salivary glands.

Complications:

- Oral candidiasis
- Gum inflammation.
- Taste disturbance.
- Difficulty swallowing.

2.4.2. Menopausal Gingivitis

The influence of menopause on gum inflammation has often been studied indirectly, by comparing a group of women undergoing HRT (hormone replacement therapy) with a group of women who are not [8] [9].

Three types of gingivitis are often observed:

- Menopausal gingivitis.
- Desquamative gingivitis.
- Chronic exfoliative gingivitis.

1) Menopausal gingivostomatitis

Also known as senile atrophic gingivitis, this is a relatively rare condition that occurs in women who have gone through menopause or in the period following menopause [8] (**Figure 1**).

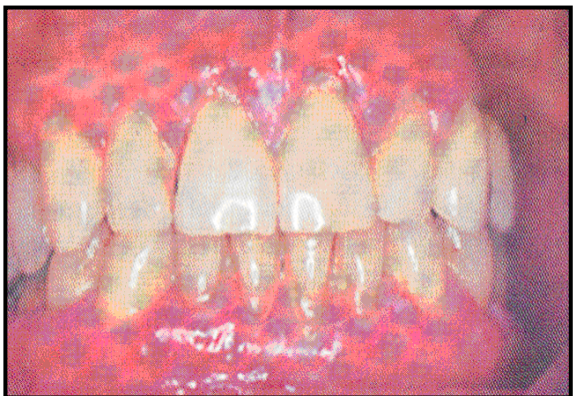

Figure 1. Atrophic gingivitis in a postmenopausal woman (M. SIDQUI).

On clinical examination, the oral mucosa appears atrophic. The gums are dry, shiny and bleed easily when brushed or probed. Their color varies from pale pink to bright red, and cracks and fissures can sometimes be triggered (ROTH) [18].

The decrease in oestrogen levels reduces the vascularisation of the connective tissue and is responsible for the atrophy.

Gram-negative bacteria and fusiform and filamentous bacteria are found in this type of gingivitis [19].

2) Desquamative gingivitis

Desquamative gingivitis is an incorrect and ambiguous term used to describe common chronic gingival lesions characterized [8] [9] [18]:

Clinically by:

- Erythema with desquamation of the free gingiva,

- Ulcerations,
- Erosions and vesicular-bullous eruptions,
- Gums varying from bright red to dark red and bleeding at the slightest trauma.

Histologically by:

- A thin epithelium.
- An alteration of the basal layer (appears atrophic or absent).
- An infiltrate of inflammatory cells in the lamina propria.

The most common causes are:

- Dermatological (lichen planus, etc.).
- Hormonal.
- Age.
- Metabolic problems.
- Chronic infection.

Bacteriology:

The bacteria responsible are not well known, but Gram-negative bacteria and fusiform and filamentous bacteria are commonly found [19].

75% of desquamative gingivitis cases are manifestations of lichen planus or pemphigus vulgaris, with the remainder related to the causes mentioned above [20] (**Figure 2**, **Figure 3**).

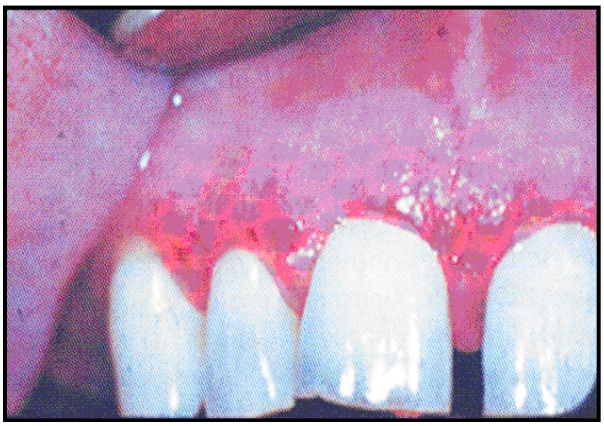

Figure 2. Desquamative gingivitis in a postmenopausal patient (M. SIDQUI).

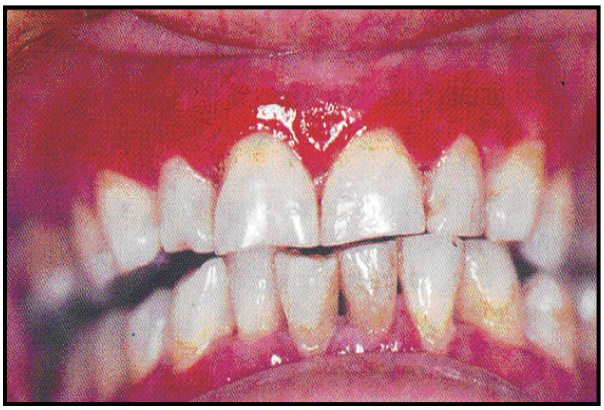

Figure 3. Desquamative gingivitis in a postmenopausal patient (M. SIDQUI).

3) Chronic exfoliative gingivitis

This is rare and occurs when menopause is established (**Figure 4**, **Figure 5**).

It is characterized by:

- Very painful erosive gums.
- Gingival bleeding.
- Dryness of the mucosa.
- Cracks, vesicles and erosions may be present.
- Mosaic erosive areas bordered by exfoliated flaps of yellowish epithelium.

The treatment for this gingivitis is purely hormonal.

For all types of gingivitis, local treatments such as chlorhexidine gels and saliva substitutes can reduce discomfort and symptoms. If these prove insufficient, it is necessary to consider a hormonal assessment (measurement of FSH, LH, oestradiol, oestrone and progesterone) in order to possibly allow for general treatment [9].

The bacteriology of chronic gingivitis is not well understood. Active plaque is composed of non-pathogenic or opportunistic bacteria such as Gram-positive cocci and bacilli. Actinomycetes and streptococci predominate in supra- and subgingival plaque. Concomitantly, there is a Gram-negative subgingival flora (*Fusobacterium nucleatum* (Fn), *Veillonella parvula* (Vp) and *Treponema* sp) [19].

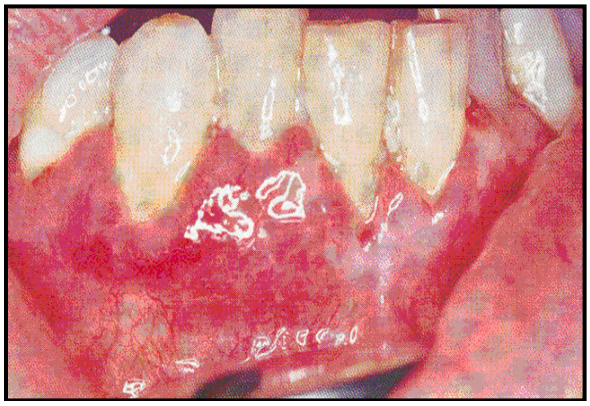

Figure 4. Exfoliative gingivitis in a postmenopausal patient (M. SIDQUI).

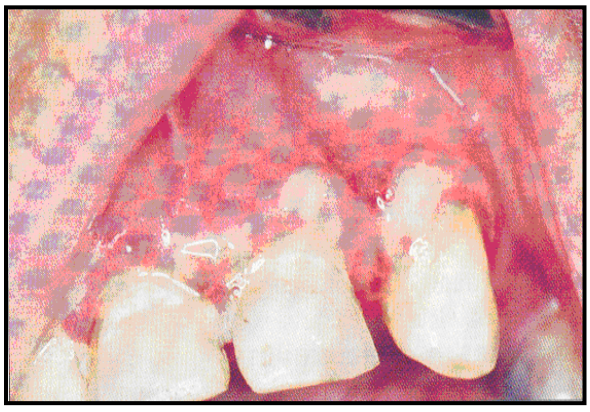

Figure 5. Exfoliative gingivitis in a postmenopausal patient (M. SIDQUI).

2.4.3. Periodontitis

1) Specific features of periodontitis in postmenopausal women:

Periodontitis is a multifactorial infectious disease in which the presence of microbial agents is only a necessary condition for the onset of the disease. Indeed, at least two other conditions must also be met: a bacterial load that inhibits key components of the host's defense mechanisms, and a response to this bacterial attack that is modified under the influence of several factors and becomes deleterious [21].

Female sex hormones influence periodontal tissues, and their fluctuations affect bacterial/host interactions in the oral cavity.

This can be due to either excess of these hormones (puberty, pregnancy, or the use of certain oral contraceptives) or, conversely, cases of deficiency resulting from a decrease or cessation of reproduction of these hormones, such as in peri- or postmenopausal women, in whom estrogen deficiency can exacerbate existing periodontitis and lead to significant and rapid destruction of the connective-epithelial attachment and bone [22].

Osteoporosis and periodontitis are two similar pathologies with certain identical etiologies and a silent mode of progression.

However, periodontitis is primarily an infectious disease, which is not the case with osteoporosis.

It is now well understood that estrogen deficiency during menopause is a significant risk factor for systemic osteoporosis.

We can then hypothesize a similar mode of action of estrogens on the maxillary bones.

Indeed, during menopause, there is a decrease in estrogen production, a decrease in the absorption of dietary calcium, and an increase in urinary calcium secretion due to the fact that estrogens are no longer sufficient to maintain existing calcium.

The major effect of estrogen deficiency is the increase in bone remodeling, which leads to alterations in the general bone structure and in particular the alveolar bone, which is of great importance for the support and stability of teeth.

These authors agree that osteoporosis could influence oral resorption and that there would be a link with periodontitis, tooth mobility, and tooth loss [23]. Indeed, osteoporosis leads to alterations in alveolar bone structure that are critical for tooth support and stability.

When estrogen deprivation affects the balance of resorption and remodeling, tooth support can be reduced, leading to clinical consequences of tooth mobility and loss [21]. The bacterial species that can be attributed an etiological role in periodontal disease are Gram-negative bacteria (*Actinobacillus actinomycetemcomitans*, *Bacteroides forsythus*, *Campylobacter rectus*, *Eikenella corrodens*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Selonomonas sputigena*, and *Treponema denticola*) and Gram-positive bacteria (*Actinomyces viscosus*, *Actinomyces naeslundii*, *Actinomyces israelii*, *Eubacterium* sp, *Peptostreptococcus* micros, *Peptostreptococcus anaerobius*, and *Streptococcus*

intermedius) [19].

The microorganisms involved in these pathologies are increasingly well understood, and their identification can aid in the diagnosis, prognosis, therapy, and reassessment of periodontal diseases [19].

2) Relationship between estrogen deficiency, osteoporosis, and periodontitis

To establish these relationships, various studies have been conducted to demonstrate:

- A relationship between estrogen deficiency and bone density loss,
- A relationship between systemic bone density loss and oral bone density loss,
- A relationship between bone density and tooth loss.

The technique used to assess bone density is bone densitometry. It measures bone mineral density (BMD) at different skeletal sites, this parameter accounts for 80% of the strength of different bone fragments [24].

Relationship between estrogen deficiency and bone density loss [21] [25]-[28]:

The amount of estrogen in women with osteoporosis may be the cause of oral bone loss in these patients, particularly if they have periodontitis.

Several studies have been conducted to demonstrate this link between estrogen deficiency and oral bone density loss.

A study by VITTEK [24] revealed that salivary estradiol concentrations are decreased or undetectable in young, postmenopausal women with periodontitis [29].

For this author, the hormone concentrations found in saliva reflect the true concentrations of circulating active hormones, *i.e.*, circulating hormones in free form.

Therefore, there appears to be a relationship between impaired steroid hormone production and an increased incidence of periodontal disease.

PAYNE [30] sought to establish a relationship between alveolar bone resorption and estrogen deficiency in postmenopausal women with or who had periodontitis.

The study group therefore included 24 women who had been postmenopausal for seven years and were divided into two groups according to their serological estrogen levels; Ten women aged 45 to 59 years comprised Group I with estrogen concentrations of 40 to 400 pg/ml and receiving hormone therapy for three years, and 14 women aged 47 to 60 years comprised Group II with estrogen concentrations of less than 35 pg/ml.

These women were healthy, had at least nine posterior teeth present in the arch, at least two sites with at least 5 mm of pockets, and at least 6 mm of clinical attachment loss.

In addition, the sites showed crestal bone loss. Using a sophisticated radiographic subtraction technique, CADIA (computer-assisted densitometric image analysis), in which a digital image is used to measure relative changes in alveolar bone density, Payne [30] demonstrated that estrogen status influences changes in alveolar bone density in postmenopausal women.

Indeed, significant differences over a one-year period were found between

estrogen-sufficient and estrogen-deficient women in the molar-molar and premolar-molar segments using bitewing radiographs.

For each of these sites, bone density was higher in estrogen-sufficient women, and a clearly significant gain in bone density was observed in these women. However, the fact that these differences are specific to the sites studied proves that estrogen is not the only factor causing density loss in these sites (knowing that premolar-molar sites do not show density differences between risk factors for periodontal disease).

Furthermore, studies on animals and humans have shown that estrogen supplementation slows bone loss by stimulating volume and density gain [30].

REINHARDT [31] conducted a study on the influence of estrogen and osteoporosis on periodontitis in postmenopausal women. He found that women with estrogen deficiency (levels below 30pg/ml) and osteoporosis show a greater incidence of sites with attachment loss and greater loss of alveolar bone density compared to women with sufficient estrogen (levels above 40pg/ml) but also with osteoporosis.

Relationship between systemic bone density and oral bone density loss [26] [32]-[35]:

KRIBBS [36] conducted a study in 85 postmenopausal women aged 50 to 84 years with osteoporosis to establish a relationship between mandibular and skeletal bone mass.

Osteoporosis was confirmed by radiographs showing fractures related to vertebral compression.

The study measured total body calcium content, radius bone mass using single-energy X-ray absorptiometry, and lumbar vertebral bone mass using dual-energy X-ray absorptiometry.

The oral assessment consists of an intraoral examination measuring the pocket depth of each tooth and taking periapical X-rays to determine mandibular bone mass using microdensitometry. The same is true of occlusal X-rays to measure mandibular bone thickness and panoramic X-rays to measure the cortical bone of the mandibular angle.

The results of this study demonstrated, in both the edentulous and dentate groups, a correlation between:

- Mandibular bone mass
- Mandibular bone density
- Cortical thickness of the mandibular angle
- With:
- Total body calcium content
- Radial and lumbar bone mass.

This correlation thus suggests that mandibular and skeletal osteopenia are linked. According to the author, mandibular bone mass is a better indicator of skeletal mass than mandibular bone density.

The height of the residual edentulous ridge is correlated with total body calcium

content, suggesting that women with severe osteoporosis retain less alveolar bone after dental extractions.

In [33], the same author repeated the same study but compared the group of women with osteoporosis to a group of postmenopausal women without radiographic or metabolic signs of bone disease.

The author found that the group of women with osteoporosis had lower mandibular bone mass and mandibular bone density than the group of normal women, as well as thinner cortical thickness of the gonion.

Furthermore, there was a greater percentage of edentulous women in the group of women with osteoporosis. The author suggested an influence of systemic osteoporosis on mandibular bone.

KRIBBS [9] evaluated alveolar ridge resorption in 355 postmenopausal women and found a correlation between overall bone loss and clinical alveolar height.

LUGAND [8] sought to establish a link between osteoporosis and oral bone loss. His study involved measuring bone mineral content in the forearm and mandible in 26 patients between 67 and 70 years of age. These women were divided into two groups: one group comparing women with fractures related to osteoporosis (Group I) and another group of women without fractures and systemic diseases (Group II) [8].

All these women were identical in terms of age at menopause and smoked the same number of cigarettes. At the dental level, the values for plaque presence and gingival bleeding are identical in all women.

The bone examination is performed using a specific technique, dual-energy absorptiometry or dual-energy CT.

The mineral content values of the mandibular bone provide representative measurements of bone mineral density related to age and sex in a part of the mandible, regardless of the state of the teeth. The values of the forearm provide a representative measurement of bone mineral density in other parts of the skeleton.

The author observed lower values for bone mineral content measurements in the forearm and mandible in women in group I compared to those in group II, and this was unrelated to the state of the teeth. Furthermore, significant attachment loss was found in women in group I.

Thus, the author concluded that there is a link between osteoporosis and oral bone loss and that a significant decrease in bone mineral density in the jaws may be associated with attachment loss in periodontal disease.

HOLST [6] established a correlation between the mineral density of the mandible and those of the femur, lumbar vertebrae, and forearm, using dual-photon X-ray absorptiometry [8].

STRECKFUS [37] conducted a study to establish a link between systemic bone density and that of the jaws.

His study measured bone density of the jaws, ulna, radius, second metacarpal, and medullary bone in 17 premenopausal women aged 20 to 48 years and in postmenopausal women aged 49 to 78. In addition, it records the values of alveolar

bone loss.

All these women are in good health and have received regular dental care.

The clinical examination does not reveal gingival bleeding or the presence of tartar.

The periodontal pockets are all less than 3 mm.

The postmenopausal women have been receiving hormone replacement therapy (consisting of 0.625 mg of sodium estrone sulfate and 10 mg of progesterone) for at least five years.

Measurements of the amount of IL-8 (a pre-inflammatory cytokine found in periodontal disease) and salivary IL-6 (a predictor of metabolic bone disease) are undertaken. The results of this study revealed that postmenopausal women have lower bone density in the maxillary, medullary, radius, and ulna bones than premenopausal women.

Furthermore, postmenopausal women have higher IL-6 levels and greater bone loss in the maxillary bones.

Bone densities of the radius, ulna, and medullary bone are strongly correlated with oral bone densities and strongly associated with menopausal status (pre- or post-menopausal) and with salivary IL-6 concentrations.

Regarding bone density measurements at the second metacarpal, these showed a strong correlation with those taken at the mandible.

Relationship between bone density and tooth loss [8] [25] [38]-[40].

They observed in 218 women aged 60 to 69 that the acquisition of dentures after the age of 50 was three times higher in women with extremely thin metacarpals [10].

In his 1992 study, he sought to establish a link between periodontitis and systemic bone mass in 248 women aged 46 to 55, 60 of whom were edentulous [38].

He measured lumbar mineral density using dual-energy absorptiometry, measured metacarpal cortical thickness using radiographs, and measured alveolar bone height in the premolar and molar segments using bitewing radiographs. These results showed that there is no correlation between clinical parameters of periodontitis and vertebral bone density measurements.

The distance between the cementum-enamel junction and the bone crest is only correlated with:

- The number of missing teeth
- Pocket depth
- Bleeding on probing
- Lumbar bone density
- Metacarpal cortical thickness.

However, he pointed out that in severe manifestations of periodontitis, a relationship with osteoporosis should not be excluded.

KRALL [39] studied the relationship between tooth loss and bone mineral density in the lumbar region, hip, and radius in 329 women aged 41 to 71 years.

These women were not taking any hormone therapy, did not have osteoporosis,

and were taking 650 mg/day of calcium. He noted a relationship between lumbar and radius bone mineral density and the total number of teeth present in women with teeth. Each tooth present represents an increase in vertebral density of 0.004 g/cm^2 and 0.003 g/cm^2 at the radius, or 0.4% and 0.5%, respectively.

Thus, systemic bone loss contributes to tooth loss.

It should be added that the number of remaining teeth is positively correlated with a high level of education and inversely correlated with age and smoking.

It was observed in 64 women aged 50 to 70 that women with a radiographic history of spinal fractures had few teeth [25].

In 1996, the same author showed that for every 1% loss of bone mineral density, the risk of losing teeth is higher. TEZAL [40] conducted a study evaluating the relationship between systemic bone loss and periodontal disease.

He measured bone density of the spine and femur using dual-energy X-ray absorptiometry (DXA) in 70 postmenopausal women aged 51 to 78 years. Women taking antibiotics and steroids, or with bone disease, cancer, or parathyroid disease were excluded.

The periodontal examination consisted of measuring dental plaque, gingival bleeding, clinical attachment loss, pocket depth, and alveolar bone height using intraoral radiography.

Bone density of the femoral and vertebral regions correlated with alveolar bone loss and clinical attachment loss. The author thus confirms, through the results of his study, the findings of previous studies: systemic osteopenia can be associated with severe periodontal disease.

In conclusion, these studies have shown that estrogen deficiency affects both the body's bones and the jawbones. This causes a loss of bone density.

Thus, in postmenopausal women, the existence of a loss of bone density aggravates pre-existing periodontitis.

The consequence is a more rapid loss of alveolar bone and therefore greater tooth loss.

2.5. Etiopathogenesis of Oral Manifestations during Menopause

2.5.1. Aging

Aging is a slowdown in the body's natural function and a loss of control over its regulation, which are characteristic of young tissues. It is a process of physiological and morphological disintegration that can be distinguished from that of childhood or adolescence, which is a process of coordination and integration. Aging manifests itself to varying degrees and in different ways depending on the organs and tissues, but it involves general transformations such as tissue dessification, reduced elasticity, decreased repair capacity, altered cellular permeability, and increased cellular calcium in many organs [41].

1) Aging of periodontal tissues

During aging, bone becomes the site of osteoporosis. Bone becomes rarer, trabeculation becomes less dense, cortices are thinned, vascularization is reduced,

resorption of small gaps is greater, and the predisposition to fractures is increased. Generalized osteoporosis is more common in older women than men and is associated with a disruption of sex hormones during aging; bone water content is reduced, crystal size is increased, and collagen fibers are thickened [41].

2) Aging of glandular tissues

Atrophic changes in the salivary glands, accompanied by the transformation of xerostomia cysts, have been associated with aging. In older experimental animals, a fatty mass appears in the salivary glands [41].

2.5.2. Psychological Cause

Menopause is a transitional period that can be difficult for some women, during which stress and depression can be common.

When faced with certain symptoms, it is necessary to assess the circumstances of their onset and the patient's degree of severity, and to understand how she perceives menopause in order to adapt treatment from both a biological and psychological perspective [9].

2.5.3. Hormonal Cause

It is well known that in women, the gums undergo changes during specific situations such as puberty, pregnancy, and the use of certain oral contraceptives, the same is true during menopause, but the manifestations are different.

These hormonal changes appear to have an effect on the gums, through mechanisms that are not yet fully understood in the current state of knowledge.

For the past thirty years, authors have attempted to provide an answer. Some have attempted to demonstrate the existence of hormone receptors in the periodontium, while others have attempted to understand the action of hormones on the various elements of the periodontium in physiological and pathological situations [9].

1) Periodontium: Target Tissue of Steroid Hormones:

For hormones to exert their biological effects in the periodontium, receptors are essential. VITTEK [29] was the first to demonstrate the presence of estrogen and progesterone receptors in gingival tissue.

To do this, he examined gingival samples from 18 patients aged 10 to 65 using a biochemical and autoradiographic method.

Ten years later, FOUREL [23], in a study on the effectiveness of HRT on oral discomfort, confirmed VITTEK's hypothesis [29], highlighting estrogen receptors in the epithelial layers of the oral mucosa and progesterone receptors in the connective tissue of the oral mucosa.

LUGAND *et al.* [35] confirmed VITTEK's theory.

PARKAR [42] refuted this theory. According to him, the techniques used by VITTEK and FORABOSCO lacked specificity. In 2000, (8) using an immunohistochemistry technique, revealed the existence of receptors in epithelial and connective tissues, in endothelial cells, and in fibroblasts of the gums of women with chronic desquamative gingivitis.

Thus, the origin of disorders in oral epithelial and connective tissues during menopause is thought to be a direct action of steroid hormones on these tissues due to the presence of receptors.

2) Hormonal Influences at the System Level

Hormonal changes influence various body systems [43]:

- Changes in the microbial flora through an increase in the number of PREVOTELLA INTERMEDIA.
- Changes at the vascular level through the dilation of gingival capillaries and an increase in the capillary permeability of venules.
- Cellular changes
- Stimulation of endothelial cells
- Decreased keratinization
- Increased epithelial glycogen
- Inhibition of collagen production
- Changes in immunity.

a) Action on immunity

The immune system, particularly polymorphonuclear leukocytes and macrophages, can be affected by altered sex hormones. This can lead to an increased susceptibility to periodontal disease [32].

Hormones also act on cytokines, which, due to their inflammatory properties, may play a role in the pathogenesis of periodontal disease.

- Action of hormones on phagocytic cells:

At the level of phagocytic cells, the presence of estrogen receptors on macrophages has been demonstrated (GULSHAN) [22]. Hormones will therefore act by modulating their action.

GULSHAN [22] demonstrated for the first time the existence of estrogen receptors on macrophages.

This helps us understand the effects of estrogen on macrophages. Estrogens are thought to increase macrophage phagocytosis activity, stimulate macrophage production of IL-1, and increase the number of blood monocytes.

This would also explain why immune responses are stronger in women than in men, and thus are more resistant to viral and bacterial infections.

However, women are thought to have more autoimmune diseases than men. Indeed, according to a study by MARKOVIC [44], since estrogens and progesterone have been shown to have immunostimulatory effects, the chronicity of high levels of these hormones during reproductive life may explain the peak incidence of autoimmune diseases in women between the ages of 40 and 60.

Estrogen receptors have also been found on CD8 T cells and mast cells. CD8 T cell activity is directly affected by estrogen (STANISZ) [45].

Since estrogen receptors have also been found on mononuclear cells and estrogen stimulates the synthesis and release of IL-1 and IL-6, this could indirectly affect B and T cells.

Furthermore, the migration and chemotaxis of polymorphonuclear leukocytes

are stimulated in the presence of estrogen (STANISZ) [45].

In a study by MIYAGI [46] on the effects of sex hormones on the chemotaxis of polymorphonuclear leukocytes and monocytes *in vitro*, progesterone had a stimulating effect on the chemotaxis of polymorphonuclear leukocytes.

Therefore, during perimenopause, when there is an endocrine imbalance (estrogen continues to be secreted while progesterone decreases), it might be thought that the decrease in progesterone results in an alteration of polymorphonuclear leukocyte chemotaxis.

Thus, altered concentrations of estrogen and progesterone can affect the immune response (STANISZ) (NORDERYD) [32] [45].

- Cytokine action:

A study by Payne [30] revealed the presence of IL-8 and IL-1β in the gingival fluid of premenopausal and postmenopausal patients with moderate to severe periodontitis. Women receiving menopausal hormone therapy (MHT) had lower IL-8 levels than other women.

IL-8 is a cytokine with inflammatory properties and neutrophil chemotaxis, and it may play a role in the pathogenesis of periodontal disease. Furthermore, IL-1β is a bone resorption cytokine; this IL-1β has been shown to stimulate IL-8 production. Reinhardt [31] compared gingival inflammation in postmenopausal patients with periodontitis, some of whom had sufficient estrogen levels (G1) and others with low levels (G2).

He found that G1 did not show an increase in inflammation.

Thus, estrogen may have an inhibitory effect on gingival inflammation in subjects with periodontitis.

This is explained by the fact that estrogen inhibits pro-inflammatory cytokines, particularly those originating from mononuclear cells.

Furthermore, the author found that in postmenopausal women with active periodontitis, gingival fluid revealed lower IL-1βlevels in women with sufficient estrogen than in those who were estrogen-deficient. Estrogens therefore inhibit the mediators and cellular mechanisms of inflammation, which explains the low incidence of bleeding on probing when plaque is high in women with sufficient estrogen.

Thus, the concentration of steroid hormones during menopause may influence the quality of immune defense during periodontal disease.

b) Action on bone tissue

Bone is one of the main targets of estrogen deficiency.

i) Bone remodeling

Bone plays two roles during resorption and formation [14] [47]:

- A metabolic role (it releases mineral salts during its destruction).
- A support role (through architectural adaptation to changes in mechanical conditions). Through interactions between osteoblasts and osteoclasts, bone remodeling consists of:
- A retraction of the lining cells protecting the extracellular matrix, allowing the arrival of osteoclasts.

- A resorption phase, mediated by osteoclasts, which degrade the extracellular matrix and form a gap.
- A phase in which osteoclasts give way to osteoblasts, which differentiate on the surface of the eroded extracellular matrix and synthesize a new matrix.

Numerous molecules act on bone cells. These include:

- Circulating molecules, hormonal (parathyroid hormone, growth hormone GH, estrogens) or non-hormonal (vitamin D, IGF1 and IGF2).
- Locally produced molecules that act through autocrine or paracrine action (IGF1 and IGF2, prostaglandin E2, IL-1, TNFα, TGFβ). Molecules present in the bone matrix (FGF2, FGFβ, IGF1, and IGF2) become active on neighboring bone cells when degradation of the extracellular matrix releases them.
- Parathyroid hormone, vitamin D, and prostaglandin E2 are osteoresorbing factors that act on osteoblasts to cause them to retract and make way for osteoclasts.

Prostaglandin E2, IGF1, IL-1, TNFα, and IL-6 promote the proliferation of osteoclast precursors present in the bone marrow, thus allowing the influx of osteoclasts during the bone resorption phase.

TGFβ decreases the proliferation of precursors into osteoclasts.

Calcitonin and prostaglandin E2 bind to receptors on the osteoclast cell membrane to inhibit bone resorption functions. In bone formation, the increase in the number of osteoblasts is a consequence of the stimulation of cell division of their precursors through the action of parathyroid hormone, FGF2, IGF2, TGF1, TGF2, TGFβ, IL-1, TNfα and to a lesser extent prostaglandin E2.

Estrogens, vitamin D, FGF2, TGFβ, IGF1, and IGF2 stimulate bone matrix production. IL-1 and TNFα inhibit it.

Bone hardness and rigidity are linked to the presence of mineral salts in the osteoid matrix.

These salts are deposited in the form of calcium and phosphate hydroxide crystals (hydroxyapatite crystals) [2]:

Osteocalcin is present in osteoid and binds extracellular calcium ions.

Alkaline phosphatase, an enzyme abundant in osteoblasts, increases calcium and phosphate ion concentrations.

Osteoblasts produce matrix vesicles that accumulate calcium and phosphate ions.

All are essential factors for ensuring a local concentration of calcium and phosphate ions, enabling mineralization [2]. Parathyroid hormone, a hormone secreted by the parathyroid glands, responds to hypocalcemia.

It stimulates bone resorption, which leads to the release of calcium ions into the blood. Furthermore, it increases serum calcium levels by reducing renal calcium ion loss and increasing intestinal absorption [2].

Calcitonin, a hormone produced by thyroid cells, is secreted in response to hypercalcemia. It has a direct effect on osteoclasts by inhibiting their resorption activity, but also on the kidneys by increasing the rate of calcium and phosphate

excretion [2].

Osteoblast proliferation and differentiation are controlled by a large number of hormones and growth factors. Hormonally controlled proliferation of osteoblastic precursors can be induced indirectly by growth factors; indeed, parathyroid hormone (PTH) has been shown to have a stimulatory effect on osteoblast production of TGFβ, IGF1/2, and IGF1-carrying proteins.

Furthermore, numerous data suggest that the stimulatory effects of sex hormones on bone matrix can be mediated by certain growth factors.

ii) Influence of estrogen deficiency on bone remodeling

The mechanisms by which estrogen deficiency during menopause abruptly triggers this increase in bone loss remain unknown; they appear complex and involve osteoblasts, osteoclasts, and bone remodeling regulatory factors (PAWLOTSKY) [48].

- Estrogens acting directly on bone:

This is explained by the presence of estrogen receptors on osteoblasts. The presence of 1,200 to 3,000 receptor sites per cell has been described. Stimulation of these receptors triggers gene transcription, with a response proportional to the stimulation. The presence of receptors on osteoclasts has also been demonstrated. Estrogens are believed to act on bone remodeling through a resorption-inhibiting action (LOPES) [3].

Osteoblasts are known to have a limited number of receptors with high affinity for estrogens, which stimulate collagen synthesis, and whose mitogenic effects on osteoblastic cells appear to be mediated by an increase in IGF1 synthesis.

Similarly, progesterone has been shown to stimulate osteoblastic proliferation and increase, at the transcriptional level, the production of IGF2.

- Estrogens acting indirectly on bone

Osteoblasts have estrogen receptors and are involved in the synthesis or activity of several cytokines and growth factors that locally modulate osteoclast activity: IL-1, IL-6, TNFα, and TGFβ (PAWLOTSKY) [48].

Estrogens can act on various molecules involved in the bone remodeling process

- On cytokines [30] [48]

Estrogen deficiency can lead to elevated concentrations of cytokines such as IL-1β (a bone resorption cytokine). Payne (1993) [30] demonstrated this in his study of 13 premenopausal and postmenopausal women (mean age 43.4 years) taking hormone therapy and 13 postmenopausal women (mean age 51.4 years) not taking hormone therapy. All of these women had moderate to severe periodontitis.

IL-1β levels in gingival fluid samples were 93.0 ± 22.8 pg/30s in women not receiving hormone therapy and 21.9 ± 13.0 pg/30s in women receiving hormone therapy.

Furthermore, IL-1b was detected in 92.3% of women not taking hormone therapy and in 23.1% of women receiving hormone therapy. The author added in his study that the production of IL-1β, IL-6, and TNFα (cytokines also involved in

bone resorption) by peripheral blood mononuclear cells is modulated by serological estrogen levels.

Recall that estrogen receptors have been identified on macrophages. In a low estrogen environment, the interaction of macrophages and bone cells with bone matrix fragments would stimulate the local production of IL-1 and IL-6, promoting bone resorption [31].

Furthermore, Reinhardt [31] analyzed the concentrations of IL-1β and IL-6 in the gingival fluid of sites with 5-6 mm pockets, clinical attachment loss of 5-7 mm, and bleeding upon probing. He demonstrated that IL-1β levels are higher in postmenopausal women without replacement therapy (92%) than in premenopausal and postmenopausal women receiving treatment (23%).

The same is true for IL-6 (in 23% of patients with estrogen deficiency and in 8% of patients with sufficient estrogen levels). These data confirm that clinical conditions that cause an estrogen-deficient environment allow for increased local production of the bone-active cytokine, IL-1β, and possibly IL-6.

For SRECKFUS [37], there is a relationship between serological estradiol levels and tissue IL-6 levels on osteoclast development and activity.

- On calcium metabolism [8]:

Estrogens can affect bone indirectly through interaction with hormones that control calcium metabolism: parathyroid hormone, calcitonin, and vitamin D.

Estrogens decrease the urinary excretion of calcium and hydroxyproline (which is an indicator of bone resorption).

It has been suggested that estrogens protect bone from parathyroid hormone, which is involved in bone resorption, and may stimulate the synthesis of vitamin D and calcitonin.

Estrogen deficiency appears to make bone more sensitive to parathyroid hormone, which increases the frequency of activation of remodeling cycles.

The increase in bone resorption leads to a slight elevation in serum calcium, which causes an increase in the decrease in parathyroid hormone secretion. Other factors such as peak bone mass in the premenopausal period and the modulating effect of estrogen on parathyroid hormone secretion and vitamin D synthesis may help explain individual susceptibility to osteoporosis [27].

iii) Action on epithelial tissue

Many authors have attempted to understand the action of hormones on the oral mucosa by comparing it to the vaginal mucosa during different stages of hormonal changes.

Indeed, during menopause, these two mucosae undergo similar changes: they become atrophied, are increasingly susceptible to infections, and women may experience a sensation of dryness. Steroid hormones act on the oral mucosa either directly through the presence of hormone receptors, or indirectly by interacting with cell growth factors (FGF, IGF1, IGF2, TNFα, TNFβ, etc.).

Steroid hormones primarily act on two groups of cells in the gingiva: fibroblasts and kyratinocytes [11].

Progesterone appears to inhibit fibroblastic gingival proliferation, while estrogen appears to stimulate fibroblast cells in culture [11].

Il a été montré que 20µg/ml de progestérone induit une diminution significative de la synthèse protéique d'au moins 50% [11].

In a study by Mariotti [11], examining healthy gingival fibroblasts from premenopausal women, physiological concentrations of estradiol stimulated cell proliferation *in vitro*.

When these cells were incubated in a medium containing estradiol concentrations ranging from 1 µM to 1 fmol, 1 µM stimulated cell proliferation significantly higher than control levels in samples of fibroblasts from premenopausal women. Furthermore, estradiol stimulated cell proliferation by 50% to 31% above normal values.

Fibroblasts from premenopausal women are considered, by some authors, notably Mariotti [11], to be a distinct cell population. Indeed, after cell activation with fluorescent markers, he identified two populations of gingival fibroblast cells, one having accumulated the marker, the other not.

Thus, it is possible that there is a subpopulation of estrogen-sensitive gingival fibroblasts in premenopausal women.

Estrogens can stimulate gingival fibroblast proliferation and connective tissue maturation primarily through their influence on collagen turnover [24].

Estrogens have stimulatory effects on collagen metabolism. They are believed to promote an increase in proline in collagen molecules in cultured skin fibroblasts [3].

Estrone is believed to exert a structural improvement in the interepithelial glycoprotein substance. It is believed to hinder the destructive action of the collagenase produced by the cells. Indeed, in the absence of estrone, collagenase dissolves the interepithelial substance, and this mechanism could also explain, through intercellular alteration, the increased tendency for hemorrhages, linked to the decrease in estrone and occurring in the marginal zones of the gingiva (ROTH) [18].

iv) Action on subgingival plaque (VITTEK)

Salivary peroxidases control the accumulation of plaque on dental surfaces and are active against a wide variety of microorganisms and bacterial toxins [29].

Thus, a decrease in the concentration of these hormones can lead to a defect in the synthesis of these enzymes, resulting in impaired defense against bacteria.

v) Action on the gingival vascular system

Estrogens are thought to have a vasodilatory effect on the arteries and increase blood flow to their target tissue. Thus, an estrogen deficiency would slow blood flow and explain the pale color of the mucosa [3].

vi) Action on the salivary glands

vi-1) Role of saliva

Saliva plays a significant role in maintaining oral health through its flow and composition. Salivary gland hypofunction can cause various symptoms such as:

root caries, periodontal disease, mucosal infections and cheilitis, taste disturbances, mucosal alterations and disturbed oral sensations [37].

This oral protection by saliva is due to the presence of non-immunological (peroxidase, lysosome, lactoferrin, etc.) and immunological (IgA, IgG, IgM) antimicrobial factors that originate from the salivary glands, serum and crevicular fluid of the marginal gingiva. IgA, IgG and IgM are antimicrobial, antifungal and antiviral factors of the mucosa [49].

Thus, one might think that an alteration in the production of these factors and/or a decrease in salivary flow would lead to the onset of symptoms in the oral cavity.

vi-2) Influence of steroid hormones on salivary composition and flow

Some authors believe that menopause causes changes in salivary flow, while others do not.

STRECKFUS *et al.* [37] did not find significant differences in salivary flow in their studies in premenopausal women, whether or not they had general and oral symptoms of menopause.

However, STRECKFUS noted that submandibular salivary flow collected after non-stimulation appears to be stable until the age of 50.

It is only when women become postmenopausal that a 33% decrease in this flow is observed. According to the author, since serological estrogen levels are not known, it is difficult to determine whether these changes are related to a decrease in estrogen or whether they are linked to age.

It is only when women become postmenopausal that a 33% decrease in this flow is observed. According to the author, since serological estrogen levels are not known, it is difficult to determine whether these changes are related to a decrease in estrogen or whether they are age-related.

Following observations by various authors, STRECKFUS [37] confirmed the existence of changes in the structure and function of the submandibular glands. This decrease could be due to a reduction in acinar cells in the glandular tissue related to an age-related increase in fibrous, adipose, and vascular tissue.

Regarding salivary composition, the study by LEIMOLA-VIRTANEN [49] shows that it is estrogen-dependent in perimenopausal and postmenopausal women. The study conducted on 27 perimenopausal and 27 postmenopausal women taking estrogen-based hormone therapy revealed that the concentrations of immunological and non-immunological antimicrobial components vary depending on several factors:

- The woman is perimenopausal.
- The woman is postmenopausal.
- The duration of hormone therapy use.

3. Conclusions

It is currently well accepted that menopause plays an important role in the onset and/or worsening of periodontitis through the action of female sex hormones on

various body systems.

However, the mechanisms of action of these hormones remain poorly understood. The psychological context in which a woman experiences menopause should not be overlooked, as it can influence the severity of the various symptoms that appear in the oral cavity: oral discomfort, menopausal gingivitis, and periodontitis. Several clinical and biochemical studies and research have proven that menopause plays a secondary role in the genesis of periodontitis, which can be avoided or at least mitigated by establishing good plaque control.

However, other studies have attributed responsibility to sex hormones in the onset of this periodontitis.

At the end of our investigation, we attempted to identify the determinants of periodontal health by comparing a group of postmenopausal women to another control group. We found that oral hygiene, the condition of the teeth, the periodontal environment, and the physiological state of menopause are the main factors responsible for periodontitis.

However, due to the association of etiological factors, the incrimination of hormonal etiology as a triggering factor should therefore be very cautious. Thus, during the menopausal transition in women and throughout the menopause period, the dental surgeon must pay particular attention to the patient's oral health and any symptoms she may experience.

For women experiencing oral symptoms during menopause, once psychological factors and local irritants have been eliminated, the dental surgeon should refer them to a doctor for a hormonal assessment. The results obtained will allow for the implementation or otherwise of general hormonal treatment.

Patients should be informed of the specifics of their condition and its impact on the oral cavity in general and the periodontium in particular.

Conflicts of Interest

The authors declare no conflicts of interest.

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