Correlation between Estrogen Deficiency and Chronic Desquamative Gingivitis in Female Patients

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Abstract- The oral mucosa may be affected by a variety of systemic diseases and oral lesions most often may precede several mucocutaneous or systemic disorders. The systemic basis for many of the oral lesions is not clearly known. One such oral disease which may have a strong systemic basis for its pathogenesis is chronic desquamative gingivitis (CDG). In the literature there are conflicting reports as to the mechanism of pathogenesis of this clinical entity. Some investigators consider this as a unique clinical disease, whereas, others consider it as the gingival manifestation of disease processes having a strong correlation with the fluctuation of female sex hormones. This study was conducted to find out a correlation between circulating levels of serum estrogen (the female sex hormone) and occurrence of CDG in female patients.

Keywords: chronic desquamative gingivitis, estrogen, hormone replacement therapy, gingivitis.

GJMR-J Classification: NLMC Code: WU 300

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Correlation between Estrogen Deficiency and Chronic Desquamative Gingivitis in Female Patients

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Abstract: The oral mucosa may be affected by a variety of systemic diseases and oral lesions most often may precede several mucocutaneous or systemic disorders. The systemic basis for many of the oral lesions is not clearly known. One such oral disease which may have a strong systemic basis for its pathogenesis is chronic desquamative gingivitis (CDG). In the literature there are conflicting reports as to the mechanism of pathogenesis of this clinical entity. Some investigators consider this as a unique clinical disease, whereas, others consider it as the gingival manifestation of disease processes having a strong correlation with the fluctuation of female sex hormones. This study was conducted to find out a correlation between circulating levels of serum estrogen (the female sex hormone) and occurrence of CDG in female patients.

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I. Introduction

As a disease entity, chronic desquamative gingivitis was first described by Tomes and Tomes in 1894. However, the term ‘desquamative gingivitis’ was first introduced by Prinz in 1932 for the presence of erythema, desquamation, erosion and blistering of attached and marginal gingiva. Glickman and Smulow stated that it is a clinical manifestation of several disorders. This is further confirmed recently by many other investigators. CDG is a clinically relevant entity as it can affect the oral health and is mainly mediated by certain hormonal deficiency states. Its clinical appearance is not significantly altered by traditional oral hygiene measures or conventional periodontal therapy. It is a fairly common complaint typically seen in females who are middle-aged or older. Many cases have also been reported in younger women, often associated with fluctuations in the circulating sex hormone levels.

CDG is a clinical condition with unclear and uncertain etiology. It is not a specific diagnosis but a descriptive term for non-specific gingival manifestation associated with different diseases. It is not a disease but represents a reaction pattern of the gingiva which conceals other pathological processes. Some investigators consider it as a specific disease, whereas, others consider it as a manifestation of immunologically mediated mucocutaneous disorder which is aggravated by local plaque accumulation and chronic irritation, or a manifestation of a number of disorders ranging from vesiculobullous diseases such as cicatricial and bullous pemphigoid, pemphigus vulgaris, erosive lichen planus, erythema multiforme, psoriasis and allergy, to adverse reaction to a variety of chemicals and allergens or manifestation of metabolic and hormonal disturbances. Though the investigators are confused about the etiology of CDG, many are of the opinion that there is a strong hormonal basis for the etiology of this condition.

It has been found that estrogen ointments when applied topically is effective in controlling this disease. Yet another therapeutic measure recommended in certain refractory cases of desquamative gingivitis is hormone replacement therapy (HRT) with low dose estrogen. However, this should be done under the careful supervision of a physician or gynaecologist. A number of studies have shown that hormone replacement therapy (HRT) with estrogen can relieve the oral discomfort in post-menopausal women, thus establishing the role of female sex hormones in the healthy maintenance of the oral tissues.

Estrogen is produced primarily in the ovaries. Some quantity of estrogen is also produced by the adrenal glands. Estrogen belongs to the category of sex steroid hormones and is a derivative of cholesterol and consists of a combination of three rings of six carbon atoms each (phenanthrene) and one ring of five carbon atoms each (cyclopentane) to form a complex hydrogenated cyclopentanoperhydrophenanthrene ring system. Signals for estrogen production originate in the pituitary gland and the levels vary throughout life depending on the stage of a woman’s menstrual cycle. The three major naturally occurring estrogens in women are estrone (E1), estradiol (E2 or 17β-estradiol or estradiol), and estriol (E3). Estradiol is the predominant estrogen during reproductive years both in terms of absolute serum levels as well as in terms of estrogenic activity. During menopause, estrone is the predominant circulating estrogen and during pregnancy estriol is the predominant circulating estrogen in terms of serum levels. Though estriol is the most plentiful of the three estrogens it is also the weakest, whereas estradiol is the strongest.
II. Review of Literature

Richman, Abarbanel, as early as 1943, realized the significance of the female sex hormone, estrogen, in the maintenance of gingival health and had used exogenous estrogen preparations to successfully treat desquamative lesions of the gingiva. They perceived that estrogens increased epithelial keratinization and stimulated proliferation of the epithelial cells.

Daniel, E, Ziskin and Zegarelli, in 1945 analyzed twelve patients, belonging to the age group of 21 to 67 years. According to them, the disease is hypothetically designated as a local manifestation of a metabolic disturbance. Various causes of this disturbed metabolism were also considered such as abnormal functioning of the thyroid gland and the interrelationship of the vitamins and estrogens. Their data suggested that a local depletion of estrogen in the oral tissues may play a major causative role. Estrogen ointments applied topically were found to be effective in controlling the disease.

Milton B. Engel et al. in 1950 had studied the pathogenesis of desquamative gingivitis and stated that the boundary between the epithelium and the connective tissue of the gingiva is formed by an optically homogeneous ground substance, which, together with the embedded fibres is termed the basement membrane. The major component of the homogeneous ground substance is an insoluble carbohydrate-protein complex which is thought to be highly polymerized. Although relatively resistant to chemical treatment, it may exhibit lability in certain physiologic and pathologic processes. The investigators are of the opinion that many of the disturbances of the gingiva originate in the connective tissue. In desquamative gingivitis, the slightest pressure of the finger or from an air blast causes a clean separation of the epithelial layer from the underlying connective tissue in an almost spontaneous manner. The gingiva is marked by many ulcerated and bleeding areas. There was degeneration of the epithelial membrane and edema and inflammation of the connective tissue. Histopathology revealed absence of basement membrane. There was increased quantity of water-soluble carbohydrate-containing substances formed due to the action of depolymerizing enzymes. A low level of estrogen might lie behind the symptoms in desquamative gingivitis as the enzymatic activity of the connective tissue is subject to hormonal influences.

Theresa Kindler in 1954 first described the Kindler syndrome which is characterized by blistering of the skin, photosensitivity, and desquamation of the gingiva. It is a rare autosomal recessive genodermatosis. Mc Carthy F. P, et al. in 1960 studied 40 cases of desquamative gingivitis over a period of 12 years and concluded that chronic desquamative gingivitis is actually a nonspecific manifestation of variety of systemic diseases. He also proposed an etiologic classification for desquamative gingivitis based on the causative factors associated with chronic desquamative gingivitis such as dermatoses, hormonal deficiencies, abnormal response to irritation, chronic infection, and idiopathic causes.

According to Glickman and Smulow in 1964, desquamative gingivitis is a disease which is primarily a degenerative process mainly affecting the gingiva. Loe in 1965 reported that gingival inflammation and hyperplasia may be associated with hormonal changes taking place during puberty, menstruation and pregnancy. Kullander and Sonesson in 1965 had reported that many oral changes can occur as a result of a decline in the estrogen levels in women. They had reported many oral changes associated with menopause. Their investigations led to the conclusion that strong relationship exists between circulating hormonal levels and inflammatory changes of the oral mucosa.

Jenson et al. in 1968 and Gorksi et al. in 1968 observed that the sex steroid hormones bind to intracellular proteins with specificity and high affinity and this concept has led to the theory that steroid hormones act via the receptors to initiate biological responses. According to Kalkwarf in 1978 and Pankhurst et al. in 1981, based on their extensive studies, have concluded that gingival inflammation may be commonly seen in women taking oral contraceptive medication. The nature of this inflammatory response of the gingiva is similar to chronic desquamative gingivitis. Therefore, they are of the opinion that chronic desquamative gingivitis may be caused by oral contraceptive medication.

Menopause and its effects on the oral health has been extensively studied by Parvinen in 1984. He is of the opinion that many oral diseases, including chronic desquamative gingivitis could be attributed to estrogen deficiency as in the case of post-menopausal state.

Green in 1986 and Greene, et al. in 1986 have identified estrogen receptors (ER) in the gingiva. Later by some other investigators the mechanism of action of estrogen-estrogen receptor was studied which led to the identification estrogen subtypes. The classical estrogen receptor (ER) was renamed ER α after the identification of ER β.

Morishita et al. in 1988 suggested that unbalanced secretion of sex hormones, i.e. an increase of estradiol and a decrease of progesterone, might be one of the factors promoting gingivitis during puberty. However, the mechanisms of the effects of these hormones in the initiation of gingival inflammation are not clearly known. Masaharu Miyagi, et al. in 1992 reported a significant positive correlation between the concentration of progesterone in the plasma of females and the chemotactic ability of polymorphonuclear leuko-
cytes (PMN) in vitro. In males, there was no significant relationship between plasma levels of sex hormones and PMN chemotactic ability. Further sex hormones had no effect on the chemotaxis of monocytes. These results suggest that the altered PMN chemotaxis associated with gingival inflammation may be due to the effects of female sex hormones. They have also stated that the gingival inflammation is exaggerated during puberty and pregnancy. Altered levels of circulating sex hormones during puberty are considered to aggravate gingivitis induced by bacterial plaque. It is generally accepted that the bacterial plaque induces gingival inflammation through interactions with host defense mechanisms. In such defense mechanisms, phagocytic cells such as PMN leukocytes and macrophages are suggested to play an important role. Therefore, they hypothesized that sex hormones may cause inflammation by their actions on the functions of PMNs or monocytes.

Ciocca and Roig in 1995\textsuperscript{25} reported the expression of RNA-m at the specific estrogen receptors by means of polymerase chain reaction (PCR) studies, through which it can be assessed whether the receptor is functional, that is whether there is genetic control or cell function control. Bonnie J. Deroo and Kenneth S. Korach in 2006\textsuperscript{26} have reviewed estrogen receptors and human disease. They have mentioned that estrogen influences many physiological processes in human, not limited to reproduction. Estrogen is also implicated in the development or progression of numerous diseases. Estrogen mediates its effect through the estrogen receptor (ER), and plays a role in the development or severity of disease. According to them estrogens induce cellular changes through several different mechanisms. In the classical mechanism of estrogen action, estrogens diffuse into the cell and binds to a protein, the estrogen receptor which is located in the nucleus.

III. **Materials and Methods**

The study was conducted in the Department of Oral Medicine and Radiology, Amrita School of Dentistry, Cochin among female patients presenting with clinical signs and symptoms of chronic desquamative gingivitis and normal subjects (the control group).

Before carrying out the study, the institutional Ethical Committee approval was obtained. Among the 100 subjects selected for the study, 50 patients with clinical presentation of chronic desquamative gingivitis were taken as the study subjects (Group A or the study group) and the remaining 50 patients without CDG were taken as control subjects (Group B or the control group).

\textbf{a) Inclusion Criteria}

The following inclusion criteria were applied while selecting the subjects of Group A:

1. Patients with clinically diagnosable chronic desquamative gingivitis.

2. Patients with normal growth pattern and secondary sexual characteristics.

3. Patients should be free from any other endocrine disorders.

4. Patients should have had normal menstrual history (in case of post-menopausal women) and the patients should have regular menstrual cycle (in patients who have not attained menopause).

5. At least one year should have elapsed after the last delivery.

6. One week should have elapsed after the last menstrual cycle.

\textbf{b) Exclusion Criteria}

The following were the exclusion criteria.

1. Patients with severe gingival inflammation attributable to local irritants such as plaque and calculus or ill-fitting prosthetic appliances.

2. Acute inflammatory conditions of the gingiva such as acute herpetic gingivostomatitis and acute necrotizing ulcerative gingivostomatitis (ANUG).

3. Patients who underwent surgical procedures of the endocrine glands or ovaries.

4. Patients on hormone replacement therapy (HRT) for any disease.

5. Patients with irregular menstrual history.

6. Patients who are pregnant or had any recent history of miscarriage.

7. Patients on hormonal contraceptives.

8. Patients with systemic contributing factors for gingival inflammation.

9. Patients who are mouth breathers.

10. Patients who are smokers.


12. Patients who are diabetic.

13. Uncooperative patients who were not willing to take part in the study.

A Proforma was prepared to record the details of the subjects included in the study. The subjects were in the age group between 25 and 60 years.

Prior to carrying out the study, the objectives of the study were explained to all the subjects in a language the subjects could understand and patient’s explicit consent was obtained in the Consent Form.

This was followed by a thorough history taking and intra oral clinical examination as outlined in the Proforma. In this study, the standard used for the clinical appearance of desquamative gingivitis included gingival erythema not resulting from plaque, gingival desquamation, other intraoral and sometimes extroral lesions, and complaints such as burning mouth after eating spicy food\textsuperscript{23, 24}. The clinical criteria also included the presentation of fiery, red, friable gingiva which is painful and desquamates easily and the involvement of buccal aspect of attached gingiva which were not significantly improved by oral hygiene measures alone. 21 Based on these clinical parameters, the free and attached gingiva...
of all the patients were examined under good illumination and after drying the surface. The serum estrogen level was estimated in all the 100 patients.

After adopting proper aseptic precautions, 4.0 ml blood was drawn from each of the subjects from the median cubital vein and immediately the sample was sent for the estimation of serum E2 level. Human serum (including serum collected in serum separator tubes) or plasma collected in lithium heparin (including plasma separator tubes) or potassium EDTA collected in glass or plastic may be used in the Architect Estradiol Assay. In the clinical laboratory, the sample thus obtained is inspected for any air bubbles. If any air bubbles are present, they are removed with a disposable applicator stick. The serum specimen is centrifuged after complete clot formation; otherwise, presence of fibrin, red blood cells or other particulate matters in the serum may cause erroneous results. The specimen may be stored for up to 7 days at 2-8°C before being estimated for serum E2 level. The sample from the middle of the tube is taken for estimation mainly to avoid any particulate matter on the top or bottom of the specimen.

The Architect Estradiol Assay is a delayed one-step immunoassay to determine the presence of estradiol in human serum and plasma using Chemiluminescent Microparticle Immuno Assay (CMIA) technology with flexible assay protocols, referred to as Chemiflex. Architect i system manufactured by Abbott Ireland, Diagnostic Division was the laboratory equipment used for the assay.

In the first step, sample, specimen diluent, assay diluent, and anti-estradiol (rabbit, monoclonal) coated paramagnetic microparticles are combined. Estradiol present in the sample binds to the anti-estradiol coated microparticles. After first incubation, estradiol acridinium labeled conjugate is added to the reaction mixture. After a second incubation, and washing, Pre-Trigger and Trigger solutions are then added and the resulting chemiluminescent reaction is measured as relative light units (RLUs). An inverse relationship exists between the amount of estradiol in the sample and the RLUs detected by the Architect optical system. The installed Estradiol assay file on the Architect i system helps to get assay parameter.

The Architect i system is loaded with the reagent kit. The reagent carousel has color coded rings which match the color bands on the reagent bottle labels. The sample is loaded. When the system runs, the sample and the reagents are loaded into the reaction vessel and measures chemiluminescent emission to determine the quantity of estradiol in the sample. The system then automatically calculates and reports the result. The estradiol test result is expressed as pg/mL. The average serum E2 level in normal menstruating females can vary from 21 to 443 pg/mL and less than 20 to 28 pg/mL, in post-menopausal women 10.

IV. Results and Observations

Group A consisted of 50 female patients belonging to the study group having clinically diagnosed chronic desquamative gingivitis and Group B consisted of 50 female subjects who were normal. Group A and Group B subjects belonged to the age group of 25 to 60 years of age. The mean age of the Group A patients was 44.52 ± 10.52. The mean age of the Group B subjects was 36.32 ± 8.32. The lowest age of the Group A patients was 25. The lowest age of the Group B subjects was 25. The highest age of the Group A patients was 60. The highest age of the Group B subjects was 60 (Table 1).

Table 1: Age of the patients across Group A and Group B samples

<table>
<thead>
<tr>
<th>AGE (in years)</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Lowest</td>
<td>Highest</td>
</tr>
<tr>
<td>44.52 ± 10.52</td>
<td>25</td>
<td>60</td>
</tr>
</tbody>
</table>

The mean serum estradiol (E2) level of the Group A patients was 18.92 ± 18.05. The mean serum estradiol (E2) level of the Group B subjects was 66.44 ± 67.48. The lowest serum estradiol (E2) level in the Group A patients was 10. The lowest serum estradiol (E2) level in the Group B patients was 10. The highest serum estradiol (E2) level in the Group A patients was 92. The highest serum estradiol (E2) level in the Group B subjects was 284 (Table 2).

Table 2: Serum E2 level across Group A and Group B samples

<table>
<thead>
<tr>
<th>SERUM E2 (in pg/ml)</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Lowest</td>
<td>Highest</td>
</tr>
<tr>
<td>18.92 ± 18.05</td>
<td>10</td>
<td>92</td>
</tr>
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In univariate analysis (Table 3), among the subject group (Group A), 60% were showing age more than 40 and in control group (Group B), 32% were showing age more than 40. The distribution of age is significantly different in subject and control groups.
There is a high percentage of low serum E2 level in Group A (80%) compared to Group B (20%) showing significant association ($p < 0.001$). Odd’s ratio is 16.0. Compared to Group B there is 16 times more chance of low level of serum E2 in Group A.

In Group A, 36% had attained menopause. In control group, 6% had attained menopause. Compared to Group B, there is 8.8 times more chance of menopause in Group A.

Multivariate logistic regression analysis was done with age, estradiol levels and menopausal status as covariates. Among these covariates, only serum E2 level was showing significant independent risk for chronic desquamative gingivitis. Odd’s ratio is 13.8 which mean 13.8 times more chance of association of chronic desquamative gingivitis with low serum E2 level.

### V. Discussion

Desquamative gingival diseases were described in the late nineteenth century by Tomes and Tomes in 1894, who noticed a singular modification of chronic inflammation of gums, in which, instead of becoming thickened and irregular on the surface, they appeared rather to decrease in size, assuming a very smooth, polished and mottled surface. The patients suffering from this complaint were poor, middle-aged women in whom menstruation was becoming irregular or had altogether ceased.

Early investigators believed gingival lesions that developed in postmenopausal women were primarily the result of a change in their hormonal status. However in the mid-twentieth century, researchers found that chronic desquamative gingivitis was probably a manifestation of several diseases with multiple etiologies. Markopoulos A. K, et al. in 1996 stated that 12% of 414 patients with desquamative gingivitis, approximately 51% were associated with mucocutaneous diseases and the rest with idiopathic or hormonal etiology. However, Crispian Scully and Stephen R. Porter in 1997, said that desquamative gingivitis is usually related to mucocutaneous disorders such as mucous membrane pemphigoid and lichen planus, chemical damage and allergic response due to mouth washes, chewing gum, or dental materials and drugs. If there are several different disease entities, the contributions of sex steroid hormones in the initiation and progression of specific desquamative lesions are largely undefined. Circumstantial clinical data are available to suggest that sex steroid hormones may play a role in some types of desquamative gingival lesions.

Hiyarasu Endo and Terry D. Rees in 2011 described the standard used for the clinical appearance of desquamative gingivitis which included gingival erythema not resulting from plaque, gingival desquamation, other intraoral and sometimes extraoral lesions, and complaints such as burning mouth after eating spicy foods. Clinically, the lesion appears as fiery red, glazed, atrophic and eroded-looking, diffuse erythema of marginal and attached gingiva with areas of desquamation and pseudo-membrane formation. Most patients with desquamative gingival lesions are middle-aged and approximately 80% are female.

The correct diagnosis of underlying disease in desquamative gingivitis patients requires careful clinical examination, detailed medical history, biopsy and histopathological examination and the more specialized tests such as direct and indirect immunofluorescence.

A number of studies suggest that oral soft tissues are sensitive to hormonal imbalance. In a study by Daniel, et al. 12 patients belonging to age group from 21 to 67 years (10 women and 2 men) were analyzed and suggested a local depletion of estrogen in
the oral tissues as a major causative agent. R.W. Wardrop, et al. in 1989 stated that oral discomfort was found to be significantly higher in peri-menopausal and post-menopausal women who reported improvement with hormone replacement therapy. Eliasson, et al. in 2003 in their study stated that HRT can relieve oral discomfort in post-menopausal women. Exogenous estrogens have been used to successfully treat desquamative lesions. This piece of evidence suggests that some lesions are estrogen sensitive and could be due to the low level of serum estrogen.

In normal menstruating females, the level of serum estrogen is 20 - 145 pg/ml during the follicular phase, 112 - 443 pg/ml during mid-cycle phase and 20-241 pg/ml during luteal phase. In post-menopausal females not on HRT, the level is 10 - 28 pg/ml.

Decreased serum estrogen level is associated with many metabolic conditions. Osteopenia, osteoporosis, and progression of periodontitis was found associated with low serum E2 level. According to Bonnie J. Deroo, et al., estrogen has wide spread role in human physiology and is implicated in the development and progression of numerous diseases, which include osteoporosis, neurodegenerative diseases, cardiovascular disease, insulin resistance, lupus erythematosus, endometriosis, obesity and various types of cancer such as breast, ovarian, colorectal, prostate and endometrial. In many of these diseases, estrogen mediates its effect through the estrogen receptor (ER), which serves as the basis for many therapeutic interventions.

Physiological and pathological response of the tissue to hormone depends on the reaction between hormone and its special receptors in the tissue because for direct response to hormone, the tissues need to have specific receptors of that hormone. The estrogen receptors are present in the non-target organs such as gingiva. The oral soft tissues are sensitive to changes in serum levels of sex steroid hormones, especially in females. According to Chebowski, et al. and Amar, et al. have stated that human gingiva can metabolize estrogen and contains specific high-affinity estrogen receptors. Masaharu Miyagi, et al. hypothesized that sex hormones may affect inflammation through their actions on the function of polymorphonuclear leukocytes (PMNs) and monocytes. In their study, the chemotactic ability of PMNs was reduced by estradiol by binding to the cytoplasmic estrogen receptors. They suggested that the altered PMN chemotaxis associated with gingival inflammation may be due to the effects of sex hormones.

Maryam Seyedmajidi, et al. stated that hormone receptors can be identified using ligand bonding, auto radiography, immunohistochemistry such as reverse transcriptase polymerize chain reaction and in situ hybridization.
that 80 % of chronic desquamative gingivitis patients (Group A) were having serum E2 level less than 20. It was only 20 % of the CDG patients who had normal serum E2 level. Whereas in control group, 80 % were with normal serum E2 level and only 20 % had decreased serum E2 level (p = 0.000). From this it is clear that there is a significant direct correlation between low level of serum E2 and the development of CDG.

Decrease in serum E2 levels was seen in all menopause patients with CDG. However, it is interesting to note that 69 % of patients with CDG, who had not attained menopause also had a decreased E2 level. This further reinforces the fact that irrespective of age and menopause, decreased E2 levels in CDG patients has a correlation with each other.

CDG in 20% of the subjects with more than 20 pg/ml may be due to idiopathic cause or may be associated with other disorders as it could be the first clinical sign and symptom in many ulcerative and vesiculobullous diseases.

In practice, long-term steroids are the mainstay for the management of CDG. Considering the side-effects of steroids, it could be beneficial to find alternative modalities of management for CDG. Hence, in cases of desquamative gingivitis not responding to steroids or in patients with low serum E2 values, topical estrogen ointments or low dose hormone replacement therapy could be considered under the careful supervision of a physician or gynaecologist.

The aim of the study was to find out if there were any correlation between CDG and serum E2 level and it is clear from the results that in 80 % of patients with CDG, serum estradiol level was low. The findings in this study should be considered as preliminary observations because only a small number of patients with CDG were analyzed. Further randomized control trials are merited to establish the linkage between low serum estradiol (E2) level and CDG. It would also help to assess treatment outcomes with estrogen supplements for patients with CDG.

**VI. Conclusion**

Desquamative gingivitis is not a disease but a reaction pattern of gingiva which conceals other pathologic diseases. Hormonal imbalance has been suggested as one of the etiology. In the present study, the level of circulating estradiol (E2) was found to be decreased in chronic desquamative gingivitis. Further investigative studies to find out the effect of exogenous estrogen in the management of desquamative gingivitis could be done. In this study, the severity of CDG and serum level of E2 was not compared. This could also be done in future studies.

**References Références Referencias**


