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Oxidative Stress in Periodontal Disease and Oral Cancer

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1. Introduction

The oral cavity is a region interconnected with other systems of the body; it should not be viewed as an isolated area. Diseases that it lays down can have systemic scope and significantly affect the quality of life of individuals who suffer them. Periodontal disease is one of the oral health problems that most often affect the global population, lack of treatment leads to loss of tooth organs and consequently alters the digestion and nutrition, without considering other relevant aspects as phonation, aesthetics and social or emotional impact. The importance of periodontal disease has raised possible bidirectional relationships with systemic diseases such as diabetes, metabolic syndrome and cardiovascular disease. We address herein the role of oxidative stress in the etiopathogeny of periodontal disease. In the same context, another disease that has become relevant in our days is the oral cancer. Epidemiological data show that the incidence of this neoplasm has been increasing in several countries. The impact of oral cancer on patients, who suffer it, is devastating. The role of oxidative stress in the development of this disease and some alternatives for its treatment, are topics addressed in this brief review. These two oral diseases are a sample of the plethora of effects that oxidative stress may have at local and systemic level.

2. Periodontal disease

Periodontitis is the second world health problem since it affects between 10 to 15% of the world population [1]. Although the various states in this disease depend on the degree of destruction and inflammation present, the American Dental Association classifies according

to a system development based on the severity of the loss of periodontal insertion. The information obtained in clinical and radiographic examination classifies the patient in four typical cases that are:

- Type I: Gingivitis
- Type II: Mild Periodontitis
- Type III: Moderate Periodontitis
- Type IV: Advanced Periodontitis

There are other classifications of the inflammatory process [2]:

- Ulceronecrotic acute gingivitis
- Acute gingivitis
- Chronic gingivitis
- Marginal periodontitis
- Superficial marginal periodontitis
- Deep marginal periodontitis

Periodontal disease is an inflammatory process involving a set of changes that directly affect tissues that hold the teeth. The etiology plays a role which is essential within the bacterial infection. In fact, within the 300 to 400 species of bacteria located in the oral cavity consider that some of them are exclusive to the periodontal tissues. However in recent years it has been determined that the evolution and spread of the disease will play a decisive role in the host response to bacterial attack. This is reflected in the model of the critical path in the pathogenesis of this disease. Through this one can understand that there are diseases and systemic conditions that have risk factors for periodontal disease, because they are going to modify the host response and favor the development of damage [3].

When it is lost in the inclusion of periodontal fibers, usually after puberty, the cases that are reported before this stage are only 5%. Previously it has reported that there was a ratio of two to one in the frequency of periodontal disease, women being the most affected in this order. Currently known, the presence by gender of this involvement is very similar.

In adults with more than 1 mm of affected dental faces periodontal insertion loss increases with age. An epidemiological report in United States mentions that approximately 80-92% of the population between the ages of 35 and 64 years performed, lost more than 1 mm insertion in 20 to 47% of teeth. From 18 to 22% of the population of 35 to 64 years were more 2 mm deep in the probing of the periodontal bags in 11 to 13% of tooth surfaces. Periodontitis occurs when tissue destruction due to the direct effect of bacterial toxins and removal products, in addition, the effects caused indirectly by the harmful organic defense mechanisms. Microorganisms as *p. gingivalis*, *a. actinomycetemcomitans* and *Capnocytophaga* sp. produce collagenase (substances similar to trypsin) and phospholipase, among others. Extracellularly

there are acid phosphatase and alkaline, lipopolysaccharides, aminopeptidase, epithelium toxin, inhibitor of fibroblasts and a toxin that induces a bone resorption.

Bacteria causes tissue destruction with its deletion, this is a feature of marginal periodontitis products. Destruction of tissues within a radius of 1.5 to 2.5 mm around the plaque has been observed (the so-called *influence radioplate*) in periodontitis. The hydrolysis of the connective tissue associated with the inflammation is due to the reactive oxygen species and the elastase/lysosomic-like enzymes. Collagenase and gelatinase are segregated to the microenvironment. Prostaglandin E, Interleukin 1-/J and the lipopolysaccharide activates osteoclasts and induce a resorption of alveolar bone. Cellular and humoral components of the immune system, mainly involved in the periodontal immune response are leukocytes, immunoglobulins, complement system and lysozyme. If the immune defenses are working properly, the periodontium is protected from the harmful effect of pathogenic substances secreted by the microorganisms. The immunocompetent host is able to defend itself against microbial attacks that occur every day. Thus prevents *infections*, i.e. the multiplication of microorganisms within the periodontium. We can say that the periodontal inflammation is a local reaction to a tissue injury whose purpose is the destruction of the causal factor, dilution or its encapsulation.

The human immune system can be classified according to their function within the periodontium, follows:

- Secretory system
- Neutrophils, antibodies and complement system
- Leukocytes and macrophages
- Immune regulation system.

The system formed by neutrophils, antibodies and complement is crucial to the immune defense against periodontal infections. When functional defects of neutrophils occur, it increases the frequency of serious marginal periodontitis [4].

3. Oxidative stress

A phenomenon that occurs within the periodontal disease is called oxidative stress. In order to understand the phenomenon of oxidative stress it is important to know what the free radicals (FR) are, where they come from and how to act. A FR is considered that molecule presented an electron unpaired or odd in the orbital external, in its atomic structure giving it a spatial configuration that generates a high instability. In the molecule of oxygen (O_2) know the following FR or also called oxygen reactive species: anion superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^{\cdot}) and singlet oxygen (1O_2). The H_2O_2 is not strictly a FR but by its ability to generate the OH^{\cdot} in the presence of metals such as iron, it incorporates it as such. A fundamental characteristic of the reactions of free radicals is that act of chain reactions, where a radical reaction generates another consecutively.

Oxygen (O_2) that this in the air is fundamental to life, many reactions in which participates the O_2 generates reactive oxygen species (ROS), of which some have the chemical character of being free radical (FR), whose biochemical entities in its atomic structure presented an odd or unpaired electron in the outer orbital, giving it a spatial configuration that generates a high instability with an enormous capacity for combined with the diversity of molecules members of the cell structure: carbohydrates, lipids, proteins, nucleic acids, and derivatives of each of them, causing important functional alterations. In this sense, the body has an antioxidant system to counteract the generation of ROS, which maintains a homeostatic balance. However there are pro-oxidant factors that favor the generation of FR, causing an imbalance in favor of the latter, generating so-called oxidative stress (OS) [5].

The tetravalent reduction of oxygen to produce water through the electron transport chain in mitochondria is relatively safe. However, the univalent reduction of oxygen generates ROS. The human organism also has antioxidant system to counteract the generation of ROS, which maintains a homeostatic balance. However, there are pro-oxidant factors that favor the generation of FR, causing an imbalance in favor of the latter, generating OS. The antioxidant enzyme superoxide dismutase (SOD), Glutathione peroxidase (GP), glutathione reductase (GR) and catalase (CAT), as well as proteins carriers of metals (ceruplasmina, transferrin, lactoferrin, etc.), and another micronutrients as vitamins A, C and E, bilirubin, uric acid and selenium, constitute the most important elements of the antioxidant system. Also, between the most important pro-oxidant factors we can highlight the process of aging, ionizing radiation, ultraviolet rays, environmental pollution, cigarette smoke, excess of exercise, intake of alcoholic beverages and inadequate diet [6].

The role of Coenzyme Q_{10} is the mitochondrial energy coupling. It is an essential part of the cellular machinery used to produce ATP that provides the energy for muscle contraction and other vital cellular functions. Most of the ATP production occurs in the inner membrane of the mitochondria, where the Coenzyme Q_{10} is located. The most important function is serving as a suppressor of primary free radicals, located in the membranes in the vicinity of unsaturated lipid chains. There are less established functions that include the oxidation/reduction of the control of the origin and transmission of signals in cells that induce the expression of gender, the control of membrane channels, the structure and solubility in lipids [7].

Free radicals cause damage to periodontal tissues by a variety of different mechanisms including:

- DNA damage
- Lipid peroxidation
- Protein damage
- The oxidation of important enzymes (anti proteases)
- Stimulation and release of pro-inflammatory cytokines

ROS covers other reactive species that are not true radicals, but are however capable of react in intra and extracellular environment: peroxide of hydrogen, hypochlorous acid, oxygen,

ozone. The living organism has adapted to an existence under a continuous output of radical free flow. Between the different antioxidant defense mechanism adaptation mechanism is of great importance. Antioxidants are "those substances that when they are present in lower concentrations compared to the substrate of an oxidizable, significantly delay or inhibit the oxidation of the substrate". The various possible mechanisms that antioxidants can offer protection against damage from free radicals are:

- The prevention of the formation of radical free.
- Interception of the radical free to eliminate reactive metabolites and their conversion to less reactive molecules.
- Facilitate the repair of the damage caused by free radicals.
- Create a favourable environment for the effective functioning of other antioxidants.

Antioxidant defense system is very dynamic and responsive to any disturbance that occurs in the body redox balance. Antioxidants can be regulated and neutralize the formation of radical free that can occur due to oxidative stress, such as the factor transcription factors Activator protein 1 and nuclear-kb are redox sensitive. Redox potential is a measure of the affinity of a substance for electrons [8].

The presence of inflammatory infiltrate is a constant feature in periodontal disease. It is known that these cells release lots of free radicals; it is suspected that these metabolites are involved in the pathogenesis of the disease. The presence of a dense inflammatory infiltrate in periodontal disease leads to the suspicion that the relationship of periodontal leukocyte-tissue has a double aspect. The role of these cells in the containment of the gingival bacteria and their products must be analyzed according to a balance with the destruction of tissue due to the release of the products of its action (FR and proteases). In this way, a defensive mechanism, under the interaction of various factors, can be harmful to periodontal tissues, and they are therefore involved in the pathogenesis of inflammatory periodontal disease.

There is numerous evidence pointing to the involvement of FR in periodontal disease. It has been reported in patients with rapidly progressive periodontitis, that the polymorphonuclear neutrophils (PMN) are functionally activated, produce high levels of O_2 and have a high response the luminol-dependent (QL) chemiluminescent. There is an increase of the PMN oxidative response peripherals in patients with localized and generalized juvenile periodontitis, as well as in adult patients with periodontitis (AP). This increase is related to clinical periodontal status and is reversed by therapy.

It has also compared the generation O_2 by the activated PMN in the gingival crevicular fluid (GCF) of patients with AP. The PMN activation with phorbolmyristateacetate causes a marked increase in the release of O_2 in patients with AP, while the antioxidant activity of the gum is similar to the controls. The effect of the PMN in crevicular fluid of patients is dependent on variations in the rate of formation of O_2 relative to the intrinsic antioxidant capacity of the gingival tissue.

In gingival epithelial cells in culture studies have shown the PMN may cause lysis of these through the action of the free myeloperoxidase(MPO), a leukocyte enzyme generating radi-

cal. Its activity has been increased in the crevicular fluid of sites with gingivitis and periodontitis with respect to healthy sites.

There is a close relationship between free radical production by leukocytes and activation of proteases. Altogether these actions could have profound effects on the function and integrity of the gingival epithelium.

The above evidence leads to consider that in the inflammatory periodontal disease, the general etiological factors causing the breakup of physiological systems of inhibition of lipid peroxidation, creates a low level of antioxidant protection of periodontal tissues. In these circumstances, the local factors lead to the migration of neutrophils to the gingiva and gingival fluid. The activation of these leukocytes in phagocytosis, causes the release of ROS, which leads to the outbreak of the lipid peroxidation of the soft tissues of the periodontium and activation of protease. This lipid peroxidation is the mechanism that triggers the development of morphofunctional changes in periodontium and their vessels, which results in destruction of collagen and bone resorption.

Due to numberless evidences that suggest a participation of the ROS in the pathogenesis of the periodontal disease, it has been raised that the factors that promote a rupture of the antioxidant physiological system, contribute to the development of oxidative mechanisms that initiate the periodontitis. The main cause of lipid peroxidation in the periodontal disease seems to lie in the liberation of ROS by leukocytes in phagocytosis. These concepts emphasize the utility of antioxidants in the prophylaxis and treatment of periodontal disease and therefore justify the search of new antioxidant preparations for this purpose. For example the *p. gingivalis* is a major cause of periodontitis, and their presence is a risk factor for systemic inflammatory syndromes, such as atherosclerosis and cardiac dysfunction. The capacity of the virulence factors such as proteases and LPS to induce inflammation has been studied intensely. In some cases, however, the inflammation occurs regardless of these factors, suggesting the existence of other stimulating immune. It was found that the cell death induced by *p. gingivalis* in the tissues is through the production of ROS [9].

4. Oral Cancer

The oral cancer occupies 2-5 % of all whole body cancers. This percentage places this neoplasia within the ten most common cancers [10]. Although its magnitude is relatively low, its impact on affected patients and their costs in health systems is high. There is a considerable variation in the incidence and mortality rates around the world. The incidence is greater in south of India, Australia, North of America, many European countries, Brazil, certain countries of Africa and some of central Asia [11]. 90% of oral cancer is of epithelial origin and the rest 10% are distributing in adenocarcinomas, sarcomas, lymphoproliferative disorders, metastasis, melanomas and malignant odontogenic tumors. The intraoral main site of oral squamous cell cancer (OSCC) is the posterior lateral border of tongue (Figure 1) and floor of mouth (Figure 2). If the lips are considered within the oral territory, then this site has the

highest frequency (Figure 3). Since oral squamous cell carcinoma (OSCC) is the main malignant neoplasia we focus in it.



Figure 1. Squamous cell cancer of the posterior lateral border of the tongue in a 28-year-old woman. She smoked a cigarette per day for 15 years.



Figure 2. Squamous cell cancer of floor of mouth in a 58-year-old woman. She had a history of poorly controlled diabetes type 2 from 42 years. She also has used ill-fitting dentures since age 50. Note the linear lesion with presence of necrosis in the centre of the fissure.

There are premalignant lesions recognized like: leukoplakia, erythroplakia, oralsubmucosal fibrosis, palatal lesions of reverse cigar smoking, oral liken planus, discoid lupus erythematosus, and hereditary disorders like congenital dyskeratosis and epidermolysis bullosa, but beyond of a clinical standpoint, diverse carcinogenic molecular mechanisms have been postulated. The main target is the DNA, since mutations that occur in it generates a wide range of deleterious effects in the cell. In a very general overview, the balance between tumor suppressor genes and those genes that induce cell cycle is altered. Allowing cells to escape cell cycle control and developing an unpredictable biological behavior. Subsequently, the cells express molecules that allow them to acquire an invasive phenotype, a phenomenon known as epithelial-mesenchymal transition. Why malignant cells colonize distant sites? Is not yet fully understood, but it is the feature that makes it lethal.



Figure 3. Squamous cell cancer of the lip in a 74-year-old man. He was a farmer and consumed alcohol chronically.

Free radicals are products of the oxidation-reduction systems of the cell and its participation in cellular metabolic functions is essential for cell survival. A classic example is the electron transport chain in mitochondria. However, in what pathological conditions, free radicals can become deleterious? In fact, what are the results of its harmful effects? The involvement of free radicals in cancer development has been studied for 3 decades, and there is sufficient evidence that implicates theirs in the multistage theory of carcinogenesis. They are proposed to cause diverse DNA alterations like: punctual mutations, DNA base oxidations, strand breaks, mutation of tumor suppressor genes and can induce overexpression of proto-oncogenes [12]. It should be added that oxidative protein damage participates in facilitating the development of cancer.

Several works explore the levels of oxidative stress in patients with oral cancer [13-15] most of them quantified the products of lipid-peroxidation (mainly malonaldehyde) and contrast them with the activity of antioxidant enzymes or exogenous antioxidants levels in blood or even saliva. The results agree that there is an imbalance between the high amount of free radicals and insufficient antioxidant system activity. Added to this, some researchers have observed that high levels of lipid-peroxidation combined with low levels of thiols and antioxidant status, correlate with poor survival rate in patients with oral cancer [16].

The OSCC is a multifactorial disease, however, a factor strongly associated, is smoking. 90% of individuals with oral cancer are smokers. It is considered that the smoke from cigarettes have 4000 chemicals, 40 of which have carcinogenic potential. It has been shown that cigarette smoke contains pro-oxidants that are capable of initiating the process of lipid-peroxidation and deplete levels of antioxidants from the diet [17,18].

In contrast, there is epidemiological evidence that demonstrates the protective effect of diet on some populations [19-21]. For example in Greece, which has the lowest rates of oral cancer among European countries, its population is exposed to latent risk factors such as alcohol intake and smoking; micronutrients consumed such as riboflavin, magnesium and iron correlated inversely with oral cancer [19].

Consequently, several authors have proposed the ingestion of diverse exogenous antioxidants; supporting in those epidemiological studies, where the diet offers protection for the development of cancer, and taking into account that the endogenous antioxidant systems have been overwhelmed by oxidative stress.

For example, vitamin C is one of the most extensively evaluated antioxidants in oral cancer alternative co-therapies. Low or even undetectable levels of vitamin C correlate with the presence of oral cancer [17, 22]; in contrast, is one of the micronutrients that have a consistent inverse correlation in different studies [23]. Vitamin C acts as a scavenger of free radicals and impedes the detrimental chain reactions triggered by the free radicals. The L-glutamine is another antioxidant that has shown a beneficial modulating effect in patients with oral cancer in stages III and IV. The L-glutamine is administered in the diet as a complementary therapy; the proposal is that restores glutathione cascade system [15]. In addition, other antioxidants such as carotene, vitamin E, thiamine, vitamin B₆, folic acid, niacin and potassium have shown a convincing protective effect [24]. Even more, when they are administered together during the cycles of radiotherapy [25].

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