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Chapter

Periodontal Medicine: Impact of Periodontal Status on Pregnancy Outcomes and Carcinogenesis

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Abstract

Periodontal medicine is a broad term commonly used to define the relationship between periodontitis and systemic health. Periodontitis is a highly prevalent, chronic multifactorial infectious disease, induced by the dysbiotic biofilm that triggers a persistent systemic inflammation and recurrent bacteremia. There is a growing body of scientific evidence that suggests the potential implication of periodontitis in the causation and progression of various systemic disease and conditions, such as diabetes, cardiovascular disease, pulmonary disease, adverse pregnancy outcomes and cancer. Some studies consider periodontitis as an independent risk factor for preterm birth, growth restriction, low birth-weight and pre-eclampsia. However not all studies support the association. Despite sparse scientific data, some studies indicate that individuals with periodontitis are at increased risk for cancer development, due to the increased inflammatory burden sustained by the presence of periodontal pathogens. This chapter emphasis the relationship between periodontitis and adverse pregnancy outcomes and the underlying mechanisms that link peridontitis to oral carcinogenesis.

Keywords: periodontitis, periodontal medicine, adverse pregnancy outcomes, preterm birth, malignancy, carcinogenesis, head, neck squamous cell carcinoma

1. Introduction

1.1 Periodontitis - overview

Periodontitis is a chronic disease, determined by the dysbiotic biofilm that does not merely affect the oral cavity, but also impacts the systemic health by triggering a persistent low-grade, systemic inflammation and recurrent bacteriemia. Its clinical consequences, especially in extended and severe forms, impair the overall quality of life of the individuals.

Significant progress has been made in determining the relationship between periodontitis and various systemic diseases. Some researchers consider periodontitis as an independent risk factor that mediates the development and even progression of certain systemic disease. Conversely, specific systemic diseases and conditions have a negative impact on the periodontium and can even interfere with periodontitis' progression. Valuable information are available with respect to several mechanisms underlying the correlation between periodontitis and systemic conditions. However, there are still plenty of issues, for which the scientific literature cannot currently provide specific answers, emphasizing their complexity and the need for further research in this area of interest.

1.2 Information search strategy and article selection

We conducted a search on the electronic database MEDLINE (PubMed) using MeSH terms and key words to identify relevant studies published between January 2011 and November 2020. One search strategy included the following subject terms combination: (["periodontitis"] OR ["periodontal disease"]) AND (["pregnancy outcome") OR ["preterm delivery"] OR ["birth weight"] OR ["pre-eclampsia"]). We searched another set of keywords as follows: (["periodontitis"]) OR ["periodontal disease"]) AND (["microbiota"] OR ["porphyromonas gingivalis"]) AND (["squamous cell carcinoma of head and neck"] OR ["head and neck neoplasms"] OR ["oropharyngeal neoplasms"] OR ["oral squamous cell carcinoma"] OR ["mouth neoplasms"]). Filters used were: Humans and English. A hand-search was also conducted to identify any additional related articles in Journal of Periodontology, Journal of Clinical Periodontology, and on the EFP Official Website/Gum disease & General Health Resources. Further articles of interest were searched based on reference lists of the publications where papers were available online. The presence of duplicates was assessed through Zotero version 5.0.93 software.

2. The periodontal medicine concept

Periodontitis is a highly prevalent, chronic multifactorial infectious disease, induced by the subgingival dysbiotic biofilm that produces a local immune-inflammatory response leading to the destruction of periodontal tissues. Its clinical manifestation, especially in extended and severe forms, impairs the overall quality of life, by affecting the psychosomatic, social and functional aspects of the individuals. Periodontitis also impacts the systemic health by triggering a persistent low-grade, systemic inflammation and recurrent bacteremia [1–4].

The concept of periodontal medicine was first introduced by Offenbacher [5]. Periodontal medicine is a broad term that describes an emerging branch of periodontology exploring the two way relationship between periodontal and systemic status, as well as new diagnostic tools and advanced treatment approaches that take into consideration the link between periodontitis and various systemic diseases [5]. Current evidence suggests that periodontitis acts as a biologically plausible risk factor for the development and progression of other chronic, inflammatory diseases [4].

Some associations between periodontitis and certain systemic conditions, such as diabetes mellitus, cardiovascular disease, and adverse pregnancy outcomes have been reported [6, 7]. However, there is still inconsistent information on the association between periodontitis and other systemic pathologies such as cancers, chronic renal disease, chronic obstructive pulmonary disease, minor cognitive impairment, rheumatoid arthritis, metabolic syndrome, and obesity [7, 8]. Contrarily, certain systemic diseases and conditions directly affect or worsen the periodontal status [9].

Establishing the potential causal relationship between periodontitis and chronic inflammatory systemic diseases and conditions is a difficult task, because complex pathologic conditions are the consequence of multiple exposures and broad interactions of external and host-derived factors that modulate disease initiation and development [1].

Noncommunicable diseases account for seven of ten worldwide deaths. In 2016, approximately 71% of the 56.9 million worldwide deaths were due to noncommunicable diseases and around 80% were due to cancers, cardiovascular diseases, chronic respiratory diseases and diabetes [10]. Since periodontitis is a potential, independent risk factor for many of these diseases, further investigations might bring additional benefits in improving the overall health status of the population and downsizing the socioeconomic burden at the same time.

3. Pathophysiological link between periodontitis and systemic diseases

Today there is increasing recognition that inflammation is a common molecular pathway that underlies the pathogenesis of diverse human diseases, ranging from infection to immune-mediated disorders, cardiovascular pathology, diabetes, metabolic syndrome, neurodegeneration, and cancer. Two pathogenic mechanisms might be involved in the activation of the pathways driving to development of pathologies at distant sites [11, 12].

The direct mechanism relies on the translocation of periodontal pathogens via systemic blood circulation, causing colonization and inflammation at a distance from the diseased periodontium. This mechanism corresponds to the concept of the "mobile oral microbiome" [13]. Moderate and severe periodontitis are characterized by deep periodontal pockets, with an ulcerated internal gingival epithelium, providing direct access for periodontal pathogens and their toxic by-products into the blood flow [12, 14]. Periodontal treatment, as well as daily tooth brushing cause episodic injuries to the periodontal tissues, which further leads to recurrent, transient bacteremia and endotoxinemia [11, 14]. On the other hand, bacterial and endotoxin dissemination may be enabled by macrophages and dendritic cells, serving as carriers for the pathogens [13, 15].

The indirect mechanism is defined by the systemic inflammatory response towards periodontal pathogens or as a result of metastatic periodontal inflammation [12, 13]. Systemic dissemination of periodontal pathogens triggers the activation of acute phase proteins in the liver, which amplify the systemic inflammatory response in order to provide protection against the bacterial threat. Acute phase protein production and the following events, as a response to periodontal infection, may affect the physiological functionality of other organs and systems. Moreover, cytokines play critical roles in orchestrating the effective immune response of leukocytes and parenchymal cells towards systemic bacteremia. Leukocytes are the major source of innate cytokine responses. A healthy immune system has the capacity to effectively eliminate pathogens and restore homeostasis. However, a dysfunctional immune response and an ineffective clearance will eventually lead to the initiation and progression of inflammatory diseases [11, 13, 14].

4. The relationship between periodontitis and pregnancy outcomes

4.1 The influence of hormonal variations in pregnancy on the periodontium

Pregnancy is characterized by significant fluctuations in the levels of progesterone and estrogen hormones reaching up to 30 times higher plasma levels, by

the end of the third trimester. Various types of periodontal cells display receptors for these hormones [16, 17], which could explain the functional changes in the periodontal cells consecutive to fluctuating hormone levels during gestation, as well as microcirculatory system alterations [18]. These modifications are triggering an increased periodontal inflammatory manifestation, even in the presence of low levels of dental plaque, especially in the second and third trimesters of pregnancy. A gradual decrease of inflammatory manifestations after parturition has been reported [16–18].

Major alterations in the maternal immune system occur during pregnancy, which could favor periodontal infection and consecutive inflammation. Pregnant women have a reduction in phagocytosis and bactericidal activities of peripheral neutrophils and changes in the monocytes stimulated secretion of proinflammatory mediators after the contact with bacterial endotoxines [16].

Pregnancy not only impacts periodontal inflammation and host immune response, but also induces an increase in the oral microbial load and modifications in the oral microbiological profiles, as a consequence of elevated levels of steroid hormones [16, 18]. Significant changes in the subgingival microbiota with increases in the proportion of some periodontal pathogens such as *Bacteroides melaninogenicus*, *Prevotella intermedia*, and *Porphyromonas gingivalis* have been described [16].

Pregnancy increases the risk of new-onset periodontal disease, but it can also activate preexisting periodontitis leading to an infectious and inflammatory load similar to new-onset periodontitis. Maternal periodontitis may reflect an intrinsic inflammatory or innate immunity trait that places the woman at risk for severe forms of periodontal disease, as well as for the common terminal biochemical inflammatory cascade associated with adverse pregnancy outcomes [19].

4.2 Epidemiological associations between periodontitis and adverse pregnancy outcomes

Many studies have associated adverse pregnancy outcomes, such as low birth weight, preterm birth and preeclampsia, with maternal periodontitis. The first case–control study referring to the relationship between periodontitis and preterm-birth reported a 7.5 higher risk ratio for preterm births for the group of women with periodontitis as compared to the periodontal healthy control group [19]. Other studies have indicated oral maternal infections, including chronic periodontitis, as potential independent risk factors for various complications throughout the pregnancy. A systematic review including case–control, cohort case-control and controlled trials, confirmed the positive association between periodontitis and adverse pregnancy outcomes [20]. A meta-analysis reported a significant association between periodontitis and preterm birth, with an odds ratio of 1.38 [21]. A more recent meta-analyses including 10.215 women, indicates that periodontitis doubles the risk for preterm delivery, the calculated odds ratio being of 2.01 (95% CI 1.71–2.36) [22]. However, the level of association is mostly modest, mainly due to the high degree of heterogeneity between the studies, particularly with respect to the diversity of periodontitis disease case definitions [23].

The relationship between periodontitis and adverse pregnancy outcomes was investigated also by means of surrogate markers defining both conditions. Many studies indicate a positive association between gingival crevicular fluid, inflammatory mediators and adverse pregnancy outcomes [23, 24].

An umbrella review which analyzed systematic reviews and meta-analysis showed that non-surgical periodontal therapy with or without antibiotic therapy has low to moderate positive effects on reducing the frequency of the common pregnancy complications related to periodontitis [25]. The large heterogeneity of

the outcomes of the interventional studies is due to variations in periodontitis case definition, sample particularities, follow-up period, control of confounding factors, as well as the therapy moment throughout the pregnancy [14, 25]. The nonsurgical periodontal therapy may be ineffective in reducing inflammatory cascade once activated and thus eventually lead to preterm birth [14].

4.3 Medical impact of adverse pregnancy outcomes

Preterm birth is defined as the birth prior to 37 weeks of gestation [26]. Complications of preterm birth are a leading cause of infant deaths worldwide raising the neonatal mortality risk rate up to 11.4 [27, 28]. The prevalence of preterm birth ranges from 5 to 7% in high-income countries, and is generally higher in low-income ones [29]. In 2014, the estimated global preterm birth rate was 10.6%, the equivalent of about 14.84 million preterm births from a total number of 139.95 million livebirths [30]. Therefore, prematurity is considered a major public health issue and the identification of any potential risk factor is of tremendous importance [27, 28, 30].

Low birth weight is defined as a birth weight below 2500 g regardless of gestational age of live infants [31, 32]. Various maternal factors such as extremes of maternal age, multiple pregnancies, obstetric complications, chronic maternal conditions like hypertensive disorders, and nutritional status or environmental exposures such as tobacco and drug use, can contribute to the low birth weight of the neonate. The estimates rate of global low birth weight for 2015 was 14.6% [31].

Maternal mortality is another important adverse outcome during pregnancy and is considered the death of a woman during pregnancy, within 42 days post-partum or during an abortion, as a consequence of any pregnancy associated pathological condition or complication [33]. The yearly number of global maternal deaths decreased from 532.000 in 1990, to 303.000 in 2015 [34]. Between 1990 and 2015, 10.7 million women worldwide died from various causes related to the evolution of pregnancy. Among the main risk factors of maternal mortality, pre-eclampsia and eclampsia are still in leading positions. Strategies aiming to reduce the number of deaths related to eclampsia showed a relatively low efficacy, which indicates the need to turn the attention to other potential risk factors in order to significantly lower mortality rates associated to eclampsia [33].

4.4 Pathophysiological link between periodontitis and adverse pregnancy outcomes

Hematogenous dissemination of periodontal bacteria is suspected to cause adverse pregnancy outcomes, by genitourinary tract and fetal–maternal unit colonization [16, 35]. Recent research indicates the presence of bacteria derived from supra- and subgingival biofilms in the placental microbiome. Moreover, some studies suggest that placental microbial profiles are closer to the oral microbial profiles than to the gut microbiome [36–38]. However, there is no general agreement on the bacterial translocation concept. The presence of oral bacteria in the placenta could be the consequence of an external contamination [39].

Although maternal infection is considered a major contributor of adverse pregnancy outcomes, a critical factor which can trigger the preterm birth might be rather the persistent inflammation generated by chronic periodontal infections. Inflammatory mediators that are abundantly produced at the affected sites determine periodontal tissue breakdown [14]. From a clinical point of view, deep periodontal pockets indicate the magnitude of the periodontal inflammation [39]. Chronic, long-term periodontal inflammation will eventually lead to a continuous

passage of cytokines, chemokines, and gingival-derived C-reactive protein from the affected periodontal tissues into the bloodstream inducing a systemic acute-phase reaction and also maintaining a chronic, systemic inflammatory status [11, 12, 14]. High levels of C reactive protein over longer periods of time increases the risk for premature birth, but also of diabetes, and cardiovascular disease. [13, 40].

Local and systemic accumulations of pro-inflammatory mediators, such as prostaglandins E2, interleukins, tumor necrosis factor α (TNF- α) and metalloproteinase (MMP) can stimulate the labor [41]. It is likely that spontaneous preterm parturition is induced by a high level of inflammation in the early stage of pregnancy [39]. However, the exact role of periodontal inflammation and the potential biological mechanisms that link periodontal disease with adverse pregnancy outcomes is not fully understood.

4.5 Clinical indications for pregnant women

European Federation of Periodontology guidelines for oral-health professionals provides the following recommendations [42]:

- During the examination of the oral status, dental professionals should always ask any female patient of childbearing age whether she is pregnant and should always consider pregnancy status before recommending any oral-health intervention.

- Inform women who are not pregnant of the importance of oral and periodontal health during pregnancy and of the treatment of existing periodontal diseases before becoming pregnant.

- For any pregnant women, perform a comprehensive clinical periodontal examination and formulate a diagnosis of “healthy”, “gingivitis”, or “periodontitis”.

- Pregnant women with a healthy periodontium should be provided with oral-health education and preventive personal plaque control measures that should became healthy habits throughout life. Also, provide information on the inflammatory periodontal events that could occur during pregnancy (increased gingival bleeding and gingival enlargement).

- Pregnant woman with gingivitis should be provided with the same oral-health education and personal plaque control measures, as well as professional mechanical instrumentation for removing plaque and calculus deposits from the tooth surfaces. The reevaluation of the periodontal status, in terms of efficacy of the professional and personal interventions and periodontal monitoring throughout pregnancy are mandatory.

- Pregnant women with periodontitis should also have the same oral-health educational measures, as well as additional professional intervention by means of standard non-surgical periodontal therapy (scaling and root planing).

- Non-surgical periodontal therapy, dental treatments and extractions are safe during pregnancy, mainly during the second trimester of gestation.

- Local anesthesia, common painkillers and systemic antibiotics are generally safe without additional risk to the foetus or the pregnant woman.

- Tetracyclines should be strictly avoided. Other medication should be prescribed to the pregnant woman after communication with her obstetrician.

- Although EFP recommends dental x-rays and chemical plaque-control agents during pregnancy, the authors of the present chapter are not keen to recommending them.

5. Implications of periodontitis in oral carcinogenesis

5.1 Epidemiological associations between periodontitis and head and neck squamos cell carcinoma

Cancer is one of the leading causes of worldwide mortality. In 2016, 1.1 million new cases were reported, and the prevalence was of 4.1 million cases. Head and neck squamous cell carcinomas (HNSCCs) constituted 5.7% of global cancer-related mortality, the equivalent of 512.770 deaths. Also the global mortality burden is expected to increase; by 2030 an estimated 705.902 people worldwide will be expected to die due to HNSCC [43]. This great burden of cancer worldwide strongly indicates the need for implementing rigorous screening and control programs in order to facilitate the identification of all potential HNSCC related risk factors, including periodontitis, and the early detection of HNSCC.

Squamous cell carcinoma is the most common histological subtype of oral and oropharyngeal malignant tumors, accounting for about 90% of the cases. The incidence of HNSCCs are reported to be on the rise, with a global estimated incidence of over 300.000 new cases registered each year [44, 45].

Emerging evidence indicates periodontitis as a potential independent risk factor for the development of premalignant lesions and HNSCC [46, 47]. Current evidence regarding a positive association between periodontitis and oral and oropharyngeal cancers are currently controversial [48]. Some studies suggest an increased susceptibility to HNSCC in periodontitis patients [49]. Extended and severe forms of periodontitis have been frequently identified among patients with HNSCC [48].

A meta-analysis reported a 2.66-fold higher risk for oral cancer in patients with periodontal disease as compared to periodontal healthy controls [50]. A hospital-based case-cohort study, after controlling for important confounders, found that individuals with periodontitis were 3.7 times more likely to have oral squamous cell carcinoma as compared to individuals without periodontitis [51].

Positive associations between periodontitis and other cancers such as digestive tract cancer, pancreatic cancer, prostate cancer, breast cancer, corpus uteri cancer, lung cancer, hematological cancer, and Non-Hodgkin lymphoma have been reported [46].

The relationship between periodontitis and HNSCC has been reported based on the specific periodontal parameters or surrogate markers of periodontal disease. An increased risk of HNSCC development, with respect to the number of missing teeth has been observed. A 2.7-fold increased risk of oral cancer in patients having 11 to 16 missing teeth as compared to dentate subjects has been reported [52]. A 5.23-fold increase in the risk of tongue cancer and a 4-fold increased risk of head and neck squamous cell carcinoma for each millimeter of alveolar bone loss, after the adjustment for important confounders has been reported [53, 54]. This data suggest that the severity and extension of periodontitis might be a risk indicator for HNSCC [55].

5.2 The influence of chronic periodontal inflammation in carcinogenesis

The investigation of the causal role of periodontitis in the cancer development is challenging due to the major independent and shared risk factors of these conditions. Periodontitis may have a direct effect on the rise of cancer risk or may impact through shared genetic and environmental factors [56]. Smoking is one of the main independent risk factors for periodontitis and HNSCC, while smoking and alcohol consumptions account for up to 85% of all oral cancers. The synergic effect of alcohol and tobacco consumption increases the risk for of oral cancer by 15 times [57, 58] However, about 15% to 20% of the HNSCCs occur independently to any of these risk factors, and the clinical features and evolution of the cancer in this group is often particularly aggressive [57–60].

Some molecular pathogenic mechanism could associate periodontitis to oral cancers and are briefly detailed below.

5.2.1 Destruction of epithelial barrier promotes the passage of toxic compounds

Chronic periodontal inflammation might be an extrinsic pathway in cancer development [46, 47, 61, 62]. The damage of the junctional epithelium mediated by periodontal pathogens alters its protective function promoting the absorption of toxic compounds from alcohol and tobacco, which in turn create a chronic inflammatory environment [61, 63]. The inflammatory process and the presence of cell-stimulating signals may create an optimal environment for the atypical cell proliferation and differentiation, which may eventually lead to cancer development [46, 61, 63].

5.2.2 Increased pro-inflammatory periodontal mediators damage DNA

In periodontitis, the complex inflammatory response developed to eliminate periodontal pathogens leads to the accumulation of excessive levels of endogenous compounds such as cytokines, chemokines, prostaglandins, reactive oxygen and nitrogen species, matrix metalloproteinases, and endothelial and epidermal growth factors. The anarchic and excessive release of these molecules is responsible for the indirect destruction of periodontal tissues [64]. In the meantime, these proinflammatory molecules may irreversibly damage the cellular DNA, deregulate the mechanisms of DNA repair and subvert the cell cycle regulatory mechanisms [65, 66]. Thus, cumulative, permanent genetic alterations lead to oncogenes activation or tumor suppressor genes inactivation [67].

5.2.3 Increased proinflammatory periodontal mediators promote epigenetic modifications

Epigenetic changes occur more frequently than gene mutations and may persist for the entire cell life and even for multiple generations. Extensive exposure of oral mucosa to bacteria and chemokines may contribute to carcinogenesis by causing epigenetic alterations. The epigenetic changes, which refer to any heritable modifications in gene expression without alterations of the DNA sequence, also promote genomic instability. Epigenetic mechanisms include DNA methylation, posttranslational modifications of histone proteins and post-transcriptional gene down-regulation by microRNAs. Any of these three distinct epigenetic mechanisms leads to inappropriate gene expression and cancer development [61, 67, 68]. A relatively stable epigenetic change may induce the increase of carcinogenesis mechanisms such as faster cellular proliferation, stimulation of an increased angiogenesis, and inhibition of apoptosis [61].

The methylation of DNA refers to the covalent addition of a methyl group to the 5-carbon position of cytosine base from a CpG dinucleotide. Hypermetilation of CpG islands of growth-regulatory genes promoter regions causes the transcriptional "silencing" of tumor suppressor genes and promotes tumor progression [68]. Although some aberrant methylation patterns have been already identified, the complex underlying molecular mechanisms that address the association of chronic periodontal inflammation and oral cancers are still not fully understood [61].

Histones, proteins binding to the DNA in the nucleus and condensing it into chromatin, can undergo multiple aberrant post-translational modifications, which induce structural and functional modification in the chromatin and thus alterations of the pattern of gene expression directly contributing to the initiation of neoplasia and its subsequent course [68].

5.2.4 The increased release of pro-inflammatory mediators

The increased release of inflammatory mediators in periodontitis, such as interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor–α (TNF–α) [61], may trigger epithelial-mesenchymal transition and activation of inflammatory cells which facilitate cancer invasion [61, 69].

5.2.5 Increased levels of IL-8 regulate carcinoma growth

IL-8 is primarily produced by periodontal cells in response to periodontal bacteria, like *Porphyromonas gingivalis*, and bacterial toxins [13, 70]. One of the possible links between *Porphyromonas gingivalis* and oral squamous cell carcinoma may be the increased IL-8 levels in the periodontal microenvironment and the subsequent overexpression of MMPs. IL-8 has long been recognized as an autocrine regulator of oral squamos cell carcinoma growth, and a contributor of increased cell motility. Thus, salivary IL-8 has been proposed to be a discriminative diagnostic biomarker for oral cancer detection [69, 70].

5.2.6 The influence of inflammasomes-mediated inflammation in cancer

More recent studies investigated the topic of inflammasome-mediated inflammation in cancer. The inflammasome is a part of the innate immune system and it responds to microbial challenge through regulation of caspase-1 activation and induction of inflammation. The most studied and best characterized inflammasome, Nucleotide-Binding Domain, Leucine-Rich–Containing Family, Pyrin Domain–Containing-3 (NLRP3), is an emerging, key player in the development and progression of cancer. Activation of NLRP3 may promote inflammation induced tumor growth and metastasis in HNSCC [71]. Certain periodontal pathogens, such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* have the ability to modulate inflammation and potentially induce carcinogenesis by controlling interleukin-1β (IL-1β) secretion through NRLP3 inflammasome complex activated by adenosine 5 '- triphosphate (ATP). IL-1β is directly involved in several chronic pathologies and various types of cancers, including oral cancer [72, 73].

5.2.7 The role of transcription factors

Inflammatory mediators, microbes, as well as environmental factors (tobacco and alcohol consumption) could activate some transcription factors, such as the nuclear signal transducers and activators of transcription-3 (STAT-3), the activator protein-1 (AP-1) and the nuclear factor-kB (NF-kB). These transcription factors

activate oncogenes that regulate apoptosis, cell proliferation and angiogenesis as well as genes regulating the production of pro-inflammatory molecules. These oncogenic changes drive a tumor-promoting inflammatory milieu through the intrinsic pathway that favors the development of already established tumors. Moreover, the inflammatory microenvironment favors the tumor to escape from immune surveillance and alters the response to chemotherapy [65, 66, 74].

5.2.8 Periodontitis associated-oxidative stress promoting carcinogenesis

Oxidative stress occurs as a state of disturbance between free radical production and the capability of antioxidant system to counteract the free radicals. The activity of periodontal bacteria induces oxidative stress through free radical release, and decreased plasma antioxidant capacity. On the other hand, oxidative stress causes inflammation, which can increase the production of free radicals. Patients with chronic periodontitis showed low serum and salivary antioxidants levels and elevated oxidative stress biomarkers such as 8-isoprostane and malondialdehyde. Moreover, assessment of blood and gingival tissues of chronic periodontitis patients also revealed mitochondrial DNA deletion mediated by lipid peroxidation [73].

Oxidative stress is also correlated to oral cancer. Increased lipid peroxidation and reduced antioxidants was reported in patients with oral cancer. Lipid peroxidation and irreversible protein modifications are essential molecular mechanisms involved in the oxidative damage of cell structures eventually leading to programmed cell death [73, 75]. Elevated levels of malondialdehyde and low levels of glutathione were observed in the saliva and serum of HNSCC patients [73, 76].

Chronic periodontal inflammation induces a prolonged exposure of oral cells to free radicals that can lead to genomic alterations through DNA damage, lipid and protein peroxidation and activation of signal transduction by post translational modification [66]. Therefore, the accumulation of oxidative stress products in periodontal tissues may significantly contribute to the development of oral cancer.

Oncogene and tumor suppressor pathways are proven intracellular targets for therapies, but recent scientific data are pointing out to new potential, *extracellular* vesicle-based therapeutic targets such as chemokines and chemokines receptors. Anti-inflammatory therapies have been successful in preventing progression and even curing some types of infectious agents associated cancers [66, 74]. Hence, control of chronic periodontal inflammation through specific periodontal therapy could be part of a comprehensive HNSCCs prevention strategy.

5.3 Periodontal bacteria in carciongenesis - *Porphyromona gingivalis*

Porphyromonas gingivalis is a true periodontal pathogen contributing in development of severe chronic inflammations of periodontal tissues. *Porphyromonas gingivalis* has been frequently associate with cancer and the most highly associated organism with oral squamous cell carcinomas [72]. Besides colonizing dental surfaces, the microorganism is also able to colonize various parts of the oral mucosa, which are described to be primary lesion sites during oral squamous cell cancer initiation [72].

Porphyromonas gingivalis produces various virulence factors which can modulate oral persistent inflammation and thus the complex physio-pathological network leading to carcinogenesis [72, 77]. *Porphyromonas gingivalis* as well as other periodontal microorganisms can trigger the development of a dysbiotic microbhabitat. *Porphyromonas gingivalis* has the capacity of disrupting the periodontal homeostasis by promoting the transformation of the commensal microbiota into a pathological

one. Also it can modulate the host's immune system, thus being able to intervene directly in the development of cancers at the oral or distant sites [78].

Porphyromonas gingivalis invades oral epithelial cells and could affect cell cycle related molecules at different stages [79]. Epithelial cell responses to *Porphyromonas gingivalis* infection include both changes to apoptosis and cell division [72, 77, 79]; these mechanisms are characteristic to cancer development and progression.

Porphyromonas gingivalis lipopolysaccharides could deregulate tumor suppressor gene p53 [72, 77]. Gingipains and cysteine proteinases produced by *Porphyromonas gingivalis*, play a key role in activating MMP-9, which degrades the basement membrane and the extracellular matrix, promoting carcinoma cell migration and invasion, thus allowing dissemination and metastatic growth at remote sites [72, 77, 78, 80]. Also in oral squamous cell carcinoma cells, *Porphyromonas gingivalis* stimulates the release of a variety of cytokines, including IL-8, which can increase MMP-9 production and cell proliferation and invasiveness [80].

Porphyromonas gingivalis can also modulate the expression of microRNAs of the epithelial cells, and up-regulation of miR-203 leads to inhibition of the negative regulator suppressor of cytokine signaling 3 and subsequent suppression of apoptosis [77].

Porphyromonas gingivalis secretes a nucleoside diphosphate kinase (NDK) having an ATPase function and preventing ATP-dependent apoptosis mediated through the purinergic receptor P2X7. Thus, NDK can suppress the proapoptotic and proinflammatory mechanisms in oral epithelial cells favoring carcinogenesis [72, 77].

The heat shock protein GroEL is another virulence factor of *Porphyromonas gingivalis* that might have a direct carcinogenic effects on certain oral cancer cell lines [72].

Porphyromonas gingivalis can induce the expression of the B7-H1 and B7-DC involved in regulating the cell-mediated immune response, but also up-regulated in cells originating from a variety of cancers. B7-H1 expression promotes the event of regulatory T cells that suppress effector T cells. B7-H1 expression might contribute to immune evasion by oral cancers [47, 77, 80].

Currently, among the known virulence molecules of *Porphyromonas gingivalis*, there is not a significantly attributed molecular determinant that could be strongly linked to the illustrated association of *Porphyromonas gingivalis* with orodigestive cancers. It is very likely that the potential synergistic ability of *Porphyromonas gingivalis* with other oral microbial species are contributory to the postulated malignant transformation and progression in the oral cavity and upper digestive tract [72].

6. Conclusions

Understanding the dynamics and common, underlying pathophysiological mechanisms that link periodontitis to systemic diseases is essential to the development of coherent, patient centered diagnostic and therapeutic strategies.

An increased risk for preterm birth and low birth weight of newborns in mothers with periodontitis has been reported. Pregnant women should be provided with oral-health education and preventive personal plaque control measures that should become healthy habits throughout life. Non-surgical periodontal therapy is safe during pregnancy, and especially during the second trimester of gestation.

The epigenetic alterations in periodontal disease such as histone acetylation and DNA methylation, and the subsequently altered gene expression might partially explain the role of periodontal inflammation in cancer development and tumor growth.

Conflict of interest

The authors declare no conflict of interest.

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