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The Role of Hypoxia in Periodontal Diseases

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Abstract

Environmental and genetic factors are effective in influencing the progression of periodontal diseases that are chronic in nature and are triggered by dysbiotic oral microbiota. Periodontal infection and inflammation are accompanied by hypoxia which is the pathological depletion of oxygen in generalized or localized tissues. Hypoxia, increases the rate of periodontal disease progression and creates related hypoxic changes in periodontal inflammation. Hypoxic changes in tissues are primarily the result of the transcriptional regulatory proteins and hypoxia induced factors. Recently, clinical studies about the relationship between hypoxia and periodontal diseases have been gaining importance throughout the literature. In the present review, we aimed to summarize the association of hypoxia and periodontal disease, depending on the evidence presented in the recent literature.

1. Periodontal Diseases

Periodontal diseases are generally recognized by the inflammation of periodontal ligament, gingiva, cementum, and alveolar bone, and are chronic in nature (Tonetti et al., 2013). They are also characterized by the dental plaque accumulation around teeth and surrounding structures and the host tissue response to the pathogens amongst dental plaque (Sun et al., 2008).

Diagnosis and the treatment of periodontal diseases can be back-traced to the ancient times. 5000 year old Egyptian and Chinese manuscripts indicate that people had had some knowledge about it (Gold, 1985). Periodontal diseases are the 6th most prevalent disease in the world and are the main cause of the tooth loss (Engebretson et al., 2003).

Gingivitis is a form of periodontal disease localized in soft tissue, which has reversible nature by the removal of bacterial dental biofilm. However; if the soft and hard tissues are both affected; meaning if the alveolar bone loss is also present; there will be irreversible consequences for the patient, and henceforth the diagnose is periodontitis (Papapanou et al., 2018).

Periodontal disease initiation and progression are associated by local, systemic and environmental factors (Engebretson et al., 2003). Plaque accumulation, which is aggravated by anatomic limitations, occlusion, and defective restorations, is considered as a local factor. Occlusal forces decrease the blood flow around periodontal ligament, which already has low vascular flow and weak physiologic nourishment intake (Kim, 1985; Ohuchi & Fujimura, 2004). In addition to occlusal factors; the other mechanical forces, such as orthodontic treatments and parafunctional habits, can deform blood vessels and cause ischemia on tissues with periodontal disease (Gölz et al., 2014).

More than 350 different gram negative anaerobic bacteria species are known to be predominant in periodontal diseases (Özer & Demiralp, 2005). Anaerobic bacterial biofilm activity also plays major role in reducing oxygen levels in affected tissue (Mettraux et al., 1984).

During the initiation and progression of the inflammation, periodontium may shift into hypoxic phase from normoxic phase (Cheng et al., 2017). Tissues that are affected by periodontal diseases reveal hypoxic and ischemic features, which are quite different from a healthy periodontal composition (Gölz et al., 2015). Also in the literature, hypoxia is defined as one of the common features of the inflammation (Cheng et al., 2017).

Studies have shown that the tobacco consumption is a major risk factor for periodontal diseases, and thus, it is generally accepted that smoking both initiates and increases the progression rate of the disease (Bergström et al., 2000; Bergström & Ellasson, 1987; Genco & Löe, 1993; Haber et al., 1993; Tomar & Asma, 2000). The main cause of the effect is the vasoconstriction generated by nicotine in tobacco products, which obstructs blood flow and prevents necessary oxygen intake for periodontal tissues (Turnbull, 1995). Carbon mono-oxide found in tobacco smoke inhibits the binding of oxygen into hemoglobin, and the end-result is the inhibition of the amount of oxygen required for tissues. Because of these side-effects, hypoxia occurs and wound healing process is inevitably hampered (Silverstein, 1992). Recent literature suggests that progression of periodontitis and oxygen insufficiency are directly related (Yu et al., 2015).

2. Oxygen Homeostasis and Hypoxia

Oxygen is required for aerobic energy metabolism and essential for producing ATP that is crucial for cell metabolic activities. Oxygen homeostasis is paramount for continuation of complex cell organisms' physiology. (Biddlestone et al., 2015) Organisms have developed a mechanism for coordinating their oxygen levels. When these mechanisms fail and cell oxygen saturation decreases, a stress related phenomenon called hypoxia occurs. Hypoxia can simply be described as the absence of oxygen required for metabolic needs. It is a physiological stress to accommodate and adapt high altitudes and/or diseases (i.e. cancer) and other similar situations (Semenza, 2000).

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Decreased oxygen concentrations, hampered organ, tissue and cell functions can be considered as hypoxic conditions (Semenza, 2001). Hypoxia is a process that occurs in tissues and cells during pathological conditions such as, romatoid arthritis, inflammatory bowel diseases, ischemia and other different chronic inflammations (Biddlestone et al., 2015; Eltzschig & Carmeliet, 2011). Oxygen pressures (mmHg) and percentages for normal circumstances and multiple hypoxia stages are summarized in Table 1. (Koh & Powis, 2012).

Organisms have developed a series of mechanisms for certain homeostatic gene activations or repressions in order to keep tissues and cells alive in hypoxic conditions. In these situations, cells produce proteins called hypoxia inducible factor (HIF), which enables necessary gene expressions from the targeted genes as a response against hypoxia (Wang et al., 1995). To this day, three types of diametrically constructed HIF proteins were identified; HIF-1, HIF-2 and HIF-3 (Koh & Powis, 2012). While having different α subunits (HIF-1α, HIF-2α, HIF-3α), their β subunit are in similar structure (Koh & Powis, 2012).

The first protein to activate hypoxia-induced gene is HIF-1α (Feldser et al., 1999). Even though HIF-1α and HIF-2α share 48% of the same characteristics, it is reported that they have tissue specific expressions and functional differences (Feldser et al., 1999). The latest discovered isoform in this class is HIF-3α and it has more pronounced dissimilarities. HIF-1α directs the hypoxia related immediate responses that are shorter than 24-hours, whereas HIF-2α is responsible of managing chronic reactions that are 24-hours or longer (Koh & Powis, 2012). During normal oxygen levels; HIF-1α is deteriorated and thus it is untraceable in cells. However, in hypoxic conditions HIF-1α shows prominent increase (Blouin et al., 2004).

In hypoxic situations, a signal pathway is activated by HIF-1. It is a transcription factor for multiple target genes that mediates biological phenomena such as angiogenesis, hematopoiesis and functions such as tissue nourishment/ regeneration for maintaining vascular tonus. HIF-1 gene enables glucose intake and regulates anaerobic respiration in an oxygen-poor environment, thus directing cellular level reactions to hypoxia (Semenza, 2011; Shay & Simon, 2012). Furthermore, by increasing vascularization, HIF-1 gene is the primary gene for maintaining homeostasis during the hypoxic conditions (Aarup et al., 2016; Shay & Simon, 2012). The most important function of the HIF-1 pathway is promoting angiogenesis and elevating the oxygen levels of hypoxic tissues. HIF-1; initiates transcription factors and affects the genes through vascular endothelial growth factor (VEGF) in order to migrate into hypoxic mediums (Carmeliet et al., 1998; Déry et al., 2005; Hewitson & Schofield, 2004). The physiologic and pathophysiologic processes are shown (Figure 1). HIF-1's physiologic activity through target genes is presented in the inner cycle and its role in diseases is represented on the outer cycle (Semenza, 2000).

3. Response of Periodontal Tissues Against Hypoxia

Pathological disturbances, like hypoxia, generally accompany periodontal infection and inflammation (Cheng et al., 2017; Takedachi et al., 2017). The initial sign of periodontal tissues' reaction to hypoxia is the increase of inflammation (Cheng et al., 2017).

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Table 1: The classification of oxygen conditions according to oxygen (O_2) levels (Koh & Powis, 2012)

Condition	pO_2 (mmHg)	% O_2
Normoxia	159	%21
Physiological hypoxia	15-68	%2-9
Mild hypoxia	8-38	%1-5
Hypoxia	<8	<%1
Anoxia	<0.08	<%0.01

Due to local inflammation, microcirculation is disrupted, and moreover induced leukocyte infiltration causes deficiency in blood and oxygen supply (Karhausen et al., 2005). In order to re-supply blood and oxygen; VEGF levels are elevated (Pradeep et al., 2011). Healthy gingiva has reportedly have normal oxygen levels, but inflamed gingiva has shown to have hypoxic levels of oxygen (Cheng et al., 2017). During inflammation, hypoxia occurs in the tissues, resulting in an increase in metabolic demands of cells and a decrease in their metabolic substrates (Kempf et al., 2005). In addition, anaerobic bacterial biofilm's development can detrimentally affect the oxygen levels as well (Mettraux et al., 1984). Hence, it can be said that low levels of oxygen in tissues initiates a response by elevating HIF-1 levels (Semenza, 2007).

In periodontitis, infiltration of inflammatory cells damage endothelium and disrupts micro vascularization, later resulting in insufficient oxygen levels in tissues (Ng et al., 2011). After that, cytokines, such as TNF-α, prostaglandin E (PGE), interleukin-1 (IL-1), IL-6, IL-8 as well as VEGF, shows increased activity (Lee et al., 2004). VEGF, being one of the most significant proangiogenic factors, is the primary element for maintaining angiogenesis.

It is originated from mesenchymal cells and recognized by specific vascular endothelial receptors (Ratcliffe, 2007). In addition, it has mitotic activity, manages cell migrations and vascular permeability. VEGF, has a significant role in physiologic and pathophysiologic neovascularization, expands the vascular network, induces angiogenesis in destroyed periodontal tissues and regulates periodontal inflammation and patients who have periodontal disease have escalated expression of this protein (Cetinkaya et al., 2007; Pradeep et al., 2011). VEGF levels are elevated, in order to prevent severe ischemic response and related damage in hypoxic tissues (Zhu & Bunn, 2001).

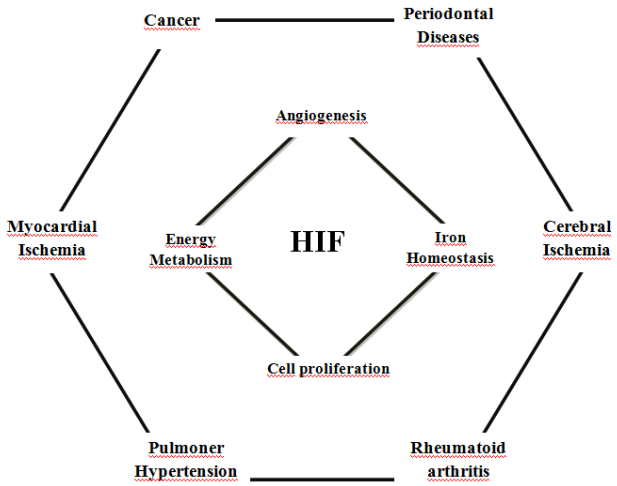

Figure 1. The physiologic and pathophysiologic processes of HIF (Semenza, 2000)

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In normoxic conditions, prolyl hydroxylase (PH) cross-links proline to the HIF-1α and HIF is degraded by ubiquitin ligase. However, in hypoxic situations, PH cannot transfer proline into HIF and denaturation of HIF is suspended, hence the accumulation of HIF occurs (Gonzalez et al., 2019). According to these facts, it may be stated that accurate detection of HIF-1α might indicate hypoxia and inflammation in periodontium (Mendes et al., 2018; Toker et al., 2018; Roseane Carvalho Vasconcelos et al., 2016). TNF-α, an important proinflammatory cytokine for periodontitis pathogenesis, can also initiate HIF-1 pathway (Haddad & Harb, 2005).

Existence of bacteria and lipopolysaccharides (LPS) in periodontal tissues directly induce HIF-1α via Toll-like receptors and cause hypoxic alterations even in the normoxic environments. Restriction of HIF-1α activity has been reported to recede inflammation (Gölz et al., 2015; Hirai et al., 2018; Kim et al., 2012; Mendes et al., 2018).

There are very limited articles on the possible association of hypoxia related markers and periodontal health, and they are mostly focused on HIF-1α. Over-expression of HIF-1α was associated with periodontitis (Afacan et al., 2019; Gonzalez et al., 2019; Ikeda, 2005). An increase in HIF-1α and VEGF levels has been reported in biopsy specimens of disease-affected periodontal tissues compared to healthy periodontal tissues (R. C. Vasconcelos et al., 2016).

4. Hypoxia in Periodontal Diseases

Inflammation and hypoxia were revealed to have an intertwined relationship (Biddlestone et al., 2015; Eltzschig & Carmeliet, 2011).

It is proposed that hypoxia carries importance as a pathogenic factor for periodontitis (Cheng et al., 2017). Literature that focuses on hypoxia and HIF-1α's effect on periodontium have shown the escalated HIF-1α expression in hypoxic human periodontal ligament cells (Agis et al., 2012; Wu et al., 2013).

Motohira et al. have studied the periodontal ligament cells on hypoxic and normoxic conditions and revealed that the hypoxic situations induce production of proinflammatory cytokines such as IL-1, IL-6 and PGE2 (Motohira et al., 2007). Hypoxic environment was also shown to increase of HIF-1α expression in human periodontal ligament cells, in vitro (Yu et al., 2015). The association with hypoxic stimulation (3% O_2) and HIF-1α expression was evaluated and HIF-1α was hardly traced in periodontal ligament cells in normoxic environment. However, periodontal ligament cells in hypoxic conditions have clearly revealed to have significantly induced HIF-1α levels (Xu et al., 2019).

The first time that elevated HIF-1α expressions were detected in diseased periodontal tissues was in 2011 (Ng et al., 2011). İn the gingival tissue samples examined by immunohistochemical methods; reported that they found significantly higher HIF-1α and VEGF levels in the periodontitis group compared to the healthy group (Ng et al., 2011).

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Matrix metalloproteinases (MMP) are zinc-containing endopeptidase group, which have collagenase, gelatinase, stromelysin. MMP's have multiple physiology like embryogenesis, inflammation, immune response, wound healing, connective tissue maturation, bone remodelling, angiogenesis and apoptosis (Nagase & Woessner, 1999).

MMP-1, -2, -3, -8 and MMP-13 have effective role in periodontal tissue destruction. (Bodden) They can also serve as markers for determining the stage of periodontitis (Ingman et al., 1996). It is proven that MMP-2 and MMP-9 influences periodontitis progression and treatment measures (Sorsa et al., 2006). It was presented that periodontal ligament cells affected by Porphyromonas gingivalis LPS in vitro, can induce HIF-1, MMP-2 and MMP-9 protein expressions directly related to the amount of LPS (Kim et al., 2012).

Karakaş et al. have compared the gingival tissue samples of smokers and non-smokers with respect to their periodontal health and have found statistically significant increase in HIF-1α levels but the amount of MMP-8 have not affected significantly (Karatas, Balci Yuce, Tulu, et al., 2019).

The elevated HIF-1α and VEGF expressions were presented to be directly related with periodontitis disease progression (Shi et al., 2015). Vasconcelos et al. results showed that the immunoexpression of HIF-1α was higher in periodontitis than in gingivitis and healthy gingiva, with statistically significant difference (R. C. Vasconcelos et al., 2016). Moreover, the peri-implantitis tissue samples shown to have significantly higher HIF-1α immune staining compared to healthy peri-implant tissues (de Araújo et al., 2017). When tissue samples of healthy individuals, as well as periodontitis, peri-implant mucositis and peri implantitis patients were examined, HIF-1α levels were observed significantly lower in healthy tissue samples and peri-implant mucositis samples had significantly lower HIF-1α expressions, compared to peri-implantitis and periodontitis groups.

Furthermore, HIF-1α levels was showed similar in both peri-implantitis and periodontitis groups. MMP-8 quantity was also found in lesser amounts in healthy groups and in similar levels between disease groups (Karatas, Balci Yuce, Taskan, et al., 2019).

Gingival crevicular fluid (GCF) has been studied by limited number of studies with the purpose of evaluating the possible associations between periodontal diseases and hypoxia. In aggressive periodontitis patients, significantly higher levels of HIF-1α and VEGF were found, compared to healthy individuals in GCF (Tayman et al., 2019). In another study, GCF HIF-1α levels were analyzed in samples from generalized aggressive periodontitis, chronic periodontitis, and gingivitis patients, as well as in the samples of healthy individuals. The results revealed that significantly higher amounts of HIF-1α, VEGF and TNF-α in GCF of aggressive and chronic periodontitis patients compared to the other groups, and concentrations of biomarkers were similar among periodontitis groups (Afacan et al., 2019). Furthermore, Afacan et al. elaborated that, 3 months after receiving initial periodontal therapy, generalized aggressive periodontitis patients have shown significantly decreased levels of HIF-1α in their GCF. However, VEGF and TNF-α have remained unchanged (Afacan et al., 2020).

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5. Conclusion

The two-way relationship between periodontal diseases and hypoxia has been broadly studied with multiple techniques throughout the literature. It is generally accepted that periodontal diseases hamper tissue nourishment while causing oxygen insufficiency.

In addition, accumulating evidence suggests that hypoxia affected by environmental and systemic factors, can also be considered as an etiological factor for periodontal disease and influences disease progression. In the present review, the studies we have presented focused on HIF and transcriptional regulatory protein activities. The interpretation of hypoxia in periodontal tissues will inevitably bring perspective on understanding disease pathogenesis and prognosis, which will later create an opportunity to understand the therapeutic potential and its association with inflammatory conditions.

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