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Role of Hypoxia on Periodontal Health

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Abstract: The opportunistic Gram-negative anaerobic bacteria at the tooth-supporting system cause human periodontitis which is a persistent inflammatory disease. The anaerobic bacteria that reside there interact with the host's inflammatory responses to create a low-oxygen or hypoxic environment within the gingivitis-affected sulcus or periodontal pocket. To help tissues adapt to fluctuations in oxygen availability caused by pathology or natural occurrences, an oxygen-sensing mechanism within each cell and within each tissue is required, as well as its proper management. In this review article, the biological significance of hypoxia with regard to periodontal/oral cellular growth, epithelial barrier function, periodontal inflammation, and immunology has been described briefly.

Keywords: Hypoxia, Chronic periodontitis, Oxygen, Inflammation, Gingivitis

Introduction: The term "periodontitis" refers to an inflammatory process that is triggered by the plaque biofilm which results in lack of periodontal adherence to the root surface and adjacent alveolar bone, eventually leading to tooth loss.[1] Although

certain, mostly gram negative anaerobic or facultative bacteria are thought to be the main cause of periodontal tissue damage in the subgingival biofilm, it is thought that most of it is brought on by an improper host reaction to those microorganisms and their byproducts.[1,2]

Hemoglobin, which is usually 97% saturated with oxygen, is where oxygen is primarily bound in our bodies. Our haemoglobin concentration is 15 g per 100 ml, therefore 100 ml of blood transports roughly 20 ml of oxygen since one gram of haemoglobin unites with 1.34 ml of oxygen. In this study, the involvement of reactive oxygen species and antioxidant defence mechanisms in the pathology of periodontitis is discussed with the goal of finding particular therapeutic targets for upcoming host-modulating therapies.In addition to being essential in all illnesses whose aetiology is linked to decreased vascularization, the utilisation of oxygen by cells rises in some morbid circumstances, such as infections.[2-4]

Various biological functions are favoured by an increase in oxygen availability to hypoxic tissues, which can be summed up as follows:

- Increase in ischemic tissue repair processes: High oxygen delivery rates boost collagen production, allowing for proper hydroxylation of this protein. Because collagen is incorrectly generated at lower tissue tensions than normal, ulcers and wounds do not heal;
- Increase in the osteogenic stimulus: In the case of fractures and osteonecrotic lesions, oxygen delivered in high volumes increases the processes of mineralization and synthesis of bone tissue.
- Antibacterial action: Oxygen delivered in high volumes has a double bactericidal action, direct and indirect.[5-6]

Hypoxia in the periodontal environment

Oxygen (O_2) is a chemical that is required for life. Humans and other mammals rely on oxygen for energy production, oxidative phosphorylation, and electron transport. Numerous physiological or pathological conditions are linked to variations in tissue oxygen requirements, therefore the tissues in question must be able to acclimate to various O_2 conditions, such as hypoxia. Mammalian cells have developed to be able to monitor and carefully control cellular O2 availability or homeostasis in order to live [7]. It is common for cells to experience hypoxia, or

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lesser than normal concentration of oxygen. This can significantly impact biological processes such as cell growth, apoptosis, pH regulation and energy metabolism, proliferation and survival, , cell migration, matrix and organelle production.[8]

Vascular endothelial growth factor are secreted by stem cells from the apical papilla under hypoxia. They improve the blood vessel network in the case of oral cellular development and regeneration. They have a role for hypoxia in the process of pulp revascularization and pulp replacements.[9-10].

Hypoxia and chronic periodontal inflammation

For healthy tissue development, appropriate tissue activities, and homeostasis, oxygen is crucial. The tissue must demand less oxygen than what would normally be needed for it to be considered hypoxic. Moderate hypoxia is defined as medium with 3-5% . [11]

Due to the inequity between tissue oxygen supply and utilization, metabolic changes under hypoxia frequently occur during the inflammatory phase of periodontitis [12]. To keep cells in a state of equilibrium, intracellular hypoxia inducible factor buildup encourages the transcription of a variety of genes.It is a dimeric protein complex and is crucial to the body's reaction to hypoxia, low oxygen levels. Hypoxia inducible factor is one of the key genes in the homeostatic mechanism, which can boost vascularization in hypoxic regions like tumours and localised ischemia. [13

In order to increase the blood flow to places like an inflammatory periodontium that need it, hypoxia causes the production of several angiogenic factors [14]. These include angioproteins 1 and 2, platelet-derived growth factor and vascular endothelial growth factor .[15] The platelet-derived growth factor receptor, cyclooxygenase-2, and nitric oxide synthase are related genes that create perfusion regulation.[16] Nitric oxide synthase governs the activities of vascular smooth muscle cells. It also responds to variations in the cellular hypoxia inducible factor level. Additionally, by switching the energy metabolism from aerobic respiration toglycolysis, hypoxia inducible factor activation encourages a metabolic transition to lower oxygen use. Pyruvate dehydrogenase kinase is also up-regulated in response to hypoxia inducible factor activation, which decreases the incorporation of pyruvate into the citric acid cycle.[17-20]

Hypoxia causes defensive cellular responses or a local defence in a chronic inflammatory condition. However, the pathophysiology of inflammation and, consequently, the aetiology of illness are influenced by these hypoxic cell interactions.[21] A comparable situation exists within the human periodontium when a person has chronic periodontitis. Periodontitis, which is caused by a number of Gram-negative anaerobic pathogens such Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, and others, is characterised by chronic inflammation of the tissues that support teeth.[22] Although oxygen consumption is enhanced and blood perfusion is encouraged, the real local microcirculation may be decreased in areas where a prolonged inflammatory reaction may be present.[23-25]

In fact, local hypoxia in periodontitis promotes the survival of anaerobic Gram-negative bacteria and further reduces the oxygen tension in the area. Increased HIF-1 protein has been linked to tissue hypoxia in periodontal disease and may be identified in tissue samples with periodontitis using Western blot and anti-HIF-1 immunostaining. [26]In the myeloid cell lineage of HIF-1-/- (deprived) animals, nitric oxide and tumour necrosis factor-alpha (TNF-) production were inhibited, which decreased their ability to fight bacteria.[27-29] Therefore, it is crucial and required for the efficient eradication of infections that immune cells be able to adjust to a reduced oxygen supply in order to maintain their monitoring capabilities in all tissue conditions.

Matrix metalloproteinases (MMPs) and proinflammatory cytokines, respectively, function as mediators of inflammation or contribute to the breakdown of extracellular matrix. In an effort to assess the level of severity of periodontitis and tracking the effectiveness of periodontal treatment, researchers frequently look into the levels of these biological markers in the periodontium [30-33]. A hypoxic environment during periodontal disease may boost the expression of proinflammatory cytokines and MMPs from host cells, according to recent studies [34]. The idea was that after being exposed to the aforementioned Gram-negative bacterial surface component, hypoxia promoted interleukin-1, and interleukin-6 (IL-6) expressions which in turn activated the nuclear factor kappa B (NF-B) pathway in human peridontal ligament cells. [34]

Periodontal epithelial cells may create matrix metalloproteinases in response to bacterial-induced activation of pathogen activated molecular patterns (PAMPs)

which leads to collagen degradation. Both the later tissue rebuilding that occurs after inflammation has subsided and the extracellular matrix disintegration that facilitates local inflammatory reactions are facilitated by these host enzymes [35,36]. The generation of nicotine-stimulated MMPs and prostaglandin E2 from periodontal ligament cells may be significantly reduced by inhibiting HIF-1 activity by chetomin. It is a chaetomium metabolite that prevents tumour cells from adapting to hypoxia, or by silencing HIF-1 gene expression. These findings raise the idea that HIF-1 could serve as a target in the periodontal tissue deterioration brought on by smoking and tooth plaque [37-40].

Regarding the healing of oral wounds, some investigations found that HIF-1 might increase or speed up the biological process in general under hypoxia [41-43]. For instance, the HIF-1 stabiliser and hydroxylase inhibitor dimethyloxalylglycine improved the healing of wounds in the rat palatal mucosa when used in a hypoxic environment, and this enzyme has been shown to promote angiogenesis that mimics hypoxia [44]. In terms of hard tissue healing, cobalt chloride induced the production of angiogenic mediators and genes associated with bone turnover, which aided in vivo fracture healing and repair [45]. The research study also shown that conditioned media obtained from dental pulp cells under hypoxia could support an angiogenic impact and bone healing during distraction osteogenesis [46].

Hypoxia and periodontal immunity

Low oxygen levels are said to modulate energy metabolism and the expression of different genes within defence cells, which in turn determine immune function and the outcomes of host protection. These hypoxic reactions, or HIF, are claimed to be highly associated to innate human responses [47]. The effects of HIF-1 and adenosine receptor modulation on T cell activities were indicative of the biological impacts of low pO2 [48]. In fact, changes in the adaptive immune response brought on by hypoxia had an impact on both lymphocytes and myeloid cells, interfering with or affecting innate immunity. After realising that pathological processes such as tumour growth, infectious locations, and wounds all entailed extremely low oxygen tension, the relevance of hypoxia in pathological processes was widely recognised.

Oral innate immunity, which has the ability to recognise, squelch, and eliminate external intruders as well as to activate future immune responses, serves as the first line of defence against periodontopathogens. Granulocytes and monocytes, or macrophages, are the two main cells for innate periodontal immunity [49, 50]. When

there is acute inflammation, these cells must go into the tissue compartment with low pO2 (i.e., the infected area) in order to provide defence and fend off the invasion. To block the invasion, the engaged innate defence cells must engage in high energy metabolism. Therefore, in order to live, it is essential that periodontal innate immune cells adapt to hypoxia and respond appropriately. The oxygen sensor HIF regulates these reactions.

To make up for the restricted oxidative metabolism under hypoxia, defence cells largely rely on glycolysis for the synthesis of ATP. The corresponding reaction appears to be considerably influenced by immune cell energy metabolism. HIF-1 is an essential regulator for the production of glycolytic enzymes, and its absence significantly lowers the amount of ATP available in myeloid cells [51-53].

HIF promotes neovascularization and the recruitment of polymorphonuclear neutrophils (PMN) to resist pathogen invasion by reviving blood supply to inflamed tissues. When there is hypoxia, the HIF restored perfusion aids in PMN diapedesis [54–55]. HIF-1 has been characterised as a safeguard in the control of its functional lifetime, which results in a decrease in PMN apoptosis under hypoxia [56–58]. This regulation of lifespan required NF-B signalling, which was found to be essential for constitutive HIF-1 protein translation. [58-59]

Although the connection between cellular stress-related transcription factor NF-B and hypoxia is not fully known, the two are strongly connected. It has been demonstrated that transforming growth factor-B-activating kinase and the inhibitor of B kinase (IKK) complex are normally active during traditional or classical NF-B activation in response to the stress of hypoxia. Through the activation of NF-B-inducing kinase hypoxia can also activate the non-canonical NF-B pathway independently of HIF-1 [60,61]. The synthesis of HIF-1 by NF-B is known to be mediated by ROS, a significant inflammatory regulator in chronic periodontal inflammation [62].

One crucial component that promotes communication between the innate and adaptive immune systems is the class of specialist antigen-presenting cells known as dendritic cells. They offer an antigen that stimulates immature cells and helps certain adaptive immune responses to infections develop. Hypoxia has been found to have a considerable impact on dendritic cell maturation and cytokine release, while the mechanism behind these linked differential effects is still up for debate [63]. Studies showed that shutting down HIF-1 in dendritic cells inhibited their maturation and

significantly decreased their ability to stimulate allogeneic T lymphocytes [64, 65]. This is because dendritic cells depend on HIF-controlled glycolysis. On the other side, it is claimed that low oxygen tension inhibited the dendritic cells' ability to protect against liposaccharides.

Since lymphocytes are known to play a role in maintaining the homeostasis of periodontal tissues, it was assumed that the disruption of lymphocyte activity was connected to periodontal pathogenesis. In a mouse model, an HIF-1 deficit was linked to aberrant B cell development that resulted in autoimmunity. [66-68]According to a recent study, the modulation of T cells by HIF-1 was largely responsible for avoiding cardiac damage in diabetic mice [67-69]. We hypothesised that diabetic periodontium might elicit a comparable defensive reaction. Hypoxia or HIF-1 regulation in DCs and lymphocytes may therefore have a substantial effect on the innate and adaptive cellular immunity in periodontal tissues, even though the precise mechanism is still unknown.

Conclusion

Combining all of the information now available, it appears that hypoxia may have either positive or negative impacts on periodontal health. At this point, we speculate that, like the intestines, the human periodontium exhibits modest levels of HIF-1 expression or low-grade hypoxia as a baseline defence or as a surveillance "alert" for periodontitis or significant invasion. Periodontal health would be maintained by an effective immune response coupled with suitable HIF-1 mediated physiologic responses. However, periodontal tissue damage could be caused by under-activation with or without corresponding dysregulation of HIF-1 biology in tissues and alveolar bone.

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