Review Article

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The Impact of Oxidative Damage on Periodontal Tissues: Addressing Implications for Periodontitis Progression and Systemic Health- A Narrative Review

Abstract:

Oxidative stress, resulting from the overproduction of reactive oxygen species (ROS), plays a significant role in the pathogenesis of periodontitis and its systemic implications. Periodontitis is a chronic inflammatory disease affecting periodontal tissues, potentially leading to tooth loss and contributing to systemic diseases such as cardiovascular disease, diabetes, chronic kidney disease, and adverse pregnancy outcomes. This review discusses the intricate relationship between oxidative stress and periodontitis, examining how ROS contribute to periodontal tissue destruction by impairing the host immune response and promoting pro-inflammatory cytokine production. Additionally, the two-way relationship between periodontitis and systemic diseases is explored, highlighting the exacerbating effect of oxidative stress on both local periodontal and systemic conditions. A deeper understanding of the role of oxidative stress in periodontal and systemic diseases can offer insights into potential therapeutic approaches and management strategies for mitigating these interconnected health issues.

Key-words: oxidative stress, periodontitis, reactive oxygen species, systemic diseases, inflammation, oral microbiota.

Introduction:

The term "oxidative stress" was coined in 1956 to describe the reaction of rubber exposed to oxygen. In the course of these studies, the term has taken on a wider meaning-the damage to cells and organs by an excess of ROS.

The term "oxidative stress" has been coined first in the work "Oxidative Stress" in 1985, as an "imbalance in the favor of prooxidants over antioxidants"[1]. In recent years, it has gradually become obvious that the processes of oxidative stress substantially influence the state of health and well-being. The final analysis is that only a balanced prooxidant-antioxidant ratio allows the possibility of redox homeostasis, or so-called "golden mean of healthy living".

"Periodontitis results from imbalance of microbial communities in periodontal tissues and is characterized by destruction of tooth-supporting structures".[2] Periodontitis is the most prevalent inflammatory disease; it might cause tooth loss in 10-15% of the population. Moreover, it might have considerable impacts on both oral and general health. The development toward periodontitis is determined by the interaction between microbial agents and host factors, including genetic susceptibility, immunological response, and the nature of the microbiota. This shift in focus away from the clinical parameters is important in understanding the pathogenesis of the disease. An imbalance in the microbial ecosystem-the dysbiosis-is the main cause for periodontitis. Therefore, it is very important that oral microbiota is balanced to show positive prevention and management of periodontitis. Timely interference with careful examination is the need for the treatment in order to restore the balance of oral microbiota and thus reduce both its severity and prevalence. The

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virulence factors of periopathogenic bacteria such as LPS, different types of proteases, and various other enzymes may interfere with the host's immune response3. Besides genetic influence, bacterial virulence factors such as fimbriae, capsules, and toxins, as well as systemic diseases like diabetes, are most likely responsible for the disease manifestation of periodontitis. Periodontitis is a disease often associated with the activation of neutrophils and may lead to ROS generation in the body's inflammatory response. Oxidative stress is such a complex process that is concerned with the overproduction of ROS. According to Rotariu et al., 2022, these ROS molecules are capable of interfering with the redox balance of the body to produce oxidative damage. All metabolisms get hampered in front of oxidative stress. ROS is responsible for tissue damage through several mechanisms, including DNA damage, protein oxidation, and initiation of LPO leading to lipid damage. [5]

Oxidative Stress and Periodontitis - A Two-way Street

There is an increasing amount of evidence to prove that reactive oxygen species are major contributors to the development of several chronic inflammatory conditions, such as (and not limited to) atherosclerosis, rheumatoid arthritis, type 2 diabetes, cancer, inflammatory lung disease, and periodontitis. These diseases are initiated by the reactive oxygen species, which form an oxidatively stressed environment. Periodontitis is an inflammatory disease that affects approximately 10% to 15% of adults and, if left untreated, leads to chronic pain and the loss of teeth and their supporting structures. The deposition of bacteria in the teeth and their migration to the nearby periodontal pocket elicits the migration of white blood cells, more specifically polymorphonuclear neutrophils, from the circulation into the site of infection. Polymorphonuclear neutrophils belong to one class of white blood cells, which is the first line of defence against bacterial pathogens seen in dental plaque. These cells represent 50%-70% of the total leukocytic infiltrate and play a very important role in periodontal health and the innate immune system. Various modes of defence include degranulation, chemotaxis, phagocytosis, NETosis, and the release of *reactive oxygen species*. However, a subset of periodontitis patients has an exaggerated "hyperactivated" polymorphonuclear neutrophil phenotype characterized by overproduction of reactive oxygen species. This is also making them more prone to the incidence of periodontitis. (6,7,8,9). This interaction between subgingival biofilm and host immune response plays an important role in the induction of dysbiosis and development of periodontitis.[10,11,12]

ROS are highly reactive molecules that can have both positive and negative effects in the body. They are essential for cell signaling, gene regulation, and antimicrobial defense but an overaproduction can lead to oxidative stress, tissue damage, and potentially tooth loss [13,14]. Intracellular ROS can damage biomolecules and cell membranes [15]. The final result of the mitochondrial respiratory burst in polymorphonuclear neutrophils in the course of phagocytosis is the generation of reactive oxygen species like $O2^{-}$, $H2O2$, and OH. These free radicals cause lipid peroxidation, damage to proteins and DNA; the imbalance leads to the activation of proinflammatory mechanisms, the formation of osteoclasts, and finally bone loss-a very common phenomenon among people suffering from periodontal disease[16,17,18, 19]. Besides affecting the density of bones, ROS also have an impact on the nuclear factor erythroid 2-related factor 2, which is considered the master antioxidant regulator[9, 20]. Therefore, it is of great importance to appreciate the role these species play in the development and progression of periodontal disease[21, 22, 23, 24]. The reactive oxygen species are associated with the high levels of proinflammatory cytokines, which mediate connective tissue and bone destruction. There is a consistent destruction of mineralized and nonmineralized tissues, although some of the products seem to be associated with the destruction of one or both types of tissues. The increase in the RANKL/osteoprotegerin ratio causes disturbance in bone remodeling, leading to the loss of bone, which is a characteristic feature of periodontitis. In addition, fibroblasts stimulated by reactive oxygen species produce less collagen, while a range of matrix metalloproteinases is excessively released at the site of infection from the host response. Such activity promotes the destruction of connective tissue and bone matrix.[25,26,27]. A high level of matrix metalloproteinases release and imbalance between these enzymes and the tissue inhibitors of matrix metalloproteinases, contribute a lot to the tissue destruction. Such cascade results in a continuous breakdown of mineral and organic matrices typical for chronic inflammatory diseases [28].

A literature review of how cytokines influence the uncoupling of bone reveals a range of proinflammatory cytokines, including interleukin-1, interleukin-6, and TNF-alpha. These cytokines promote the activity of osteoclasts, induce death in osteoblasts, and affect bone remodeling through the induction of RANKL during the destruction of periodontal tissues [28, 29]. Indeed, it was noted that the heightened concentration of some cytokines, such as interleukin-8, interleukin-6, TNF-

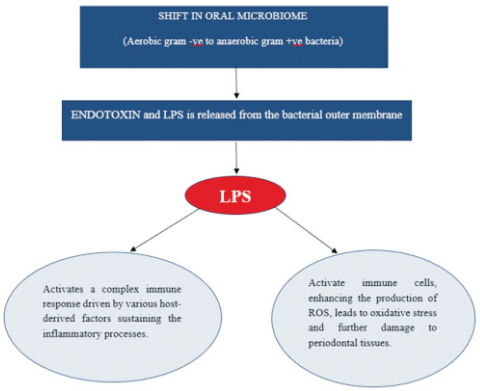
alpha, and interleukin-1beta, might be present in the hyper-responsive peripheral blood polymorphonuclear neutrophils of periodontitis patients even after non-surgical periodontal treatment[30]. It would appear that certain people have a genetic predisposition for an abnormal, often hyperactive, polymorphonuclear neutrophil phenotype that continues to show increased reactivity even after neutralization of the microbial threat.

Moreover, patients with type 2 diabetes produce significantly higher amounts of interleukin-8, interleukin-1beta, and TNF-alpha by unstimulated peripheral blood neutrophils, which may suggest increased predisposition to microbial colonization[31]. It may be a plausible cause as to why diabetic patients are more prone to periodontitis and tend to develop more severe periodontitis compared to nondiabetic patients.

Impact of Oxidative Stress on Pathogenesis Of Periodontal Disease:

The breakdown of periodontal tissue is believed to result from oxidative stress. The periodontal disease groups presented significantly higher oxidative stress in the periodontium compared to the gingivitis and healthy groups. Individuals with periodontitis had higher levels of biomarkers reflective of tissue injury produced by ROS and higher antioxidant enzyme levels considered indicative of oxidative stress in inflamed periodontal tissue and gingival fluid. [32]

Recent studies have focused on the role of ROS in periodontitis progress, especially in the programmed cell death of hPDLSCs, the movement of PDLFs, and alveolar bone loss[33]. On many occasions, ROS at appropriate concentrations was found to significantly affect cell proliferation and movement, cell death, and wound-healing processes (\[34,35].



Figur 1- Pathogenesis of Periodontal Disease

Periodontitis is caused by a change in the oral microbiome, where anaerobic Gram-negative bacteria release virulent factors like endotoxin and LPS. This triggers a complex immune response that causes inflammation, which can activate immune cells and generate bioactive molecules like ROS, leading to further damage to the periodontal tissues.

LPS and oxidative stress are factors highly influencing the periodontitis pathogenesis. It was also reported that LPS could induce the production of proinflammatory cytokines that, in turn, stimulate and sustain the recruitment and activation of immune cells for tissue damage in periodontal tissues [36].

The Interrelationship Between Periodontitis and Systemic Diseases: The Role of Oxidative Stress:

Periodontitis may induce systemic inflammation and oxidative stress, which then may be the starting point for various conditions. The presence of bacteria in inflamed gingiva and their virulence factors can cause a systemic inflammatory response after their penetration into the bloodstream. This may influence the development and course of many conditions, including cardiovascular diseases, diabetes, chronic renal disease, and liver-related pathology. This is a two-way relationship: not only does periodontal disease have negative systemic consequences, but some systemic diseases are also considered to be a risk factor for periodontal disease. This paper summarizes the systemic adverse outcomes associated with periodontal disease.

Periodontitis and Cardiovascular Diseases

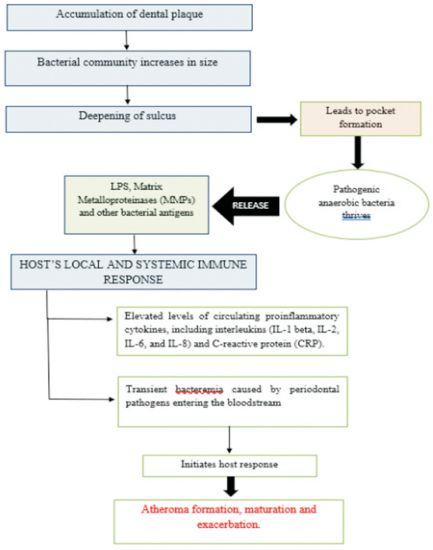


Figure 2:The Corelation Between Periodontitis And Cardiovascular Diseases

It has been suggested that the involvement of OS in enhancing cardiovascular disease is under much consideration. Furthermore, it was proposed that oxidative stress may have a role in the pathophysiological process resulting in inflammatory diseases such as cardiovascular disease and periodontitis. Periodontitis may cause systemic chronic inflammation that could impair the function of cells lining blood vessels, allowing further exacerbation of inflammation in already existing narrowings in arteries, thereby increasing the risk of cardiovascular diseases. Research has shown that ROS can initiate an immune response through their actions on redox-sensitive gene transcription factors, which include NF-κB. The result is the production of inflammatory cytokines [37]. Periodontitis has been linked to the overproduction of ROS in periodontal tissue, GCF, or gingival blood [38].

The levels of pro-inflammatory cytokines listed above have been seen to rise with the severity of periodontal disease in the body, while they decline after treatment. These same cytokines have also been detected in atheromatous lesions [39,40].

Recent studies also highlighted the existence of some well-known active pathogens in gum diseases, such as P. gingivalis, T. forsythia, A. actinomycetemcomitans, Pr. Intermedia, within arterial plaque [41,42,43].

Periodontitis And Diabetes:

Longitudinal studies have demonstrated a strong link between diabetes and periodontitis. Periodontal tissue destruction is more severe in diabetic patients. Poor glycemic control is also a common feature in individuals with diabetes and periodontal diseases [44,45]

MECHANISMS UNDERLYING THE EFFECT OF DIABETES MELLITUS ON PERIODONTITIS:

Inflammatory factors and oxidative stress:

Serum from patients with periodontitis displays elevated levels of pro-inflammatory and prothrombotic mediators like c-reactive protein, TNF-α, and IL-6. Thus, the dysregulation of peripheral cytokines is presently considered as an integral component in the pathogenesis of diabetes. For example, TNFα has been shown to induce insulin resistance through interference with the insulin signaling pathway, and circulating levels of this cytokine are elevated in individuals with periodontal disease. Periodontal disease has been reported to accelerate the deterioration of pancreatic beta-cell function in diabetic mice[46]. Systemic oxidative stress biochemical markers remained constantly higher in periodontitis and diabetes mellitus; therefore, oxidative stress and mitochondrial dysfunction are considered common factors in the pathogenesis of the two diseases[47,48]. Moreover, periodontitis patients show a positive correlation of these markers along with CRP levels[49]. Diabetes significantly heightened general oxidative damage, and diminished the capacity of the body for its defense. This led to enhanced MAD expression and lowering of superoxide dismutase activity [50, 51].

The concurrence of the establishment of periodontitis and diabetes was seen to enhance oxidative damage both in the local and systemic levels. Such a finding is well associated with enhanced destruction of periodontal tissues that are present in periodontitis patients suffering from diabetes (52).

Periodontitis and chronic kidney disease:

Among the risk factors that are shared both for periodontitis and chronic kidney disease, there could be mentioned obesity, smoking, and age [53]. The connection between periodontitis and kidney diseases had been observed more with evidence. Moreover, the latter could be influenced by the oxidative stress after periodontitis appeared [54]. The findings reported included structure and form changes to kidney tissues, damage to the microvilli in the tubules of the kidneys, and alterations associated with increased oxidative stress to the kidneys following the induction of periodontitis (55). Antioxidants have been found to act protectively against diminished liver and kidney function resulting from induced periodontal disease.[53,56]. The level of MDA within kidneys in the group with periodontitis was much higher than among animals without this condition. It was found out that the glutathione concentration in the group with periodontitis was significantly lower than in those animals that did not have periodontitis. Thus, Periodontitis could potentially elevate oxidative stress in the blood, which may result in kidney impairment.

Periodontitis and Liver Injury:

Evidence for oxidative stress causing lipid peroxidation, protein oxidation, DNA damage, and mitochondrial dysfunction in liver injury has shown that all these listed are important in this process.[57]. This antioxidant compound is known to decrease the levels of marker enzymes associated with tissue damage, including aryl hydroxylase, gamma-glutamyl transferase, and adenosine deaminase in rat liver tissue. It has also been shown to inhibit lipid peroxidation

induced by reactive oxygen species in primary rat hepatocytes (58). Thus, it seems that oxidative stress may be very crucial in liver injury.

Periodontitis and Adverse Pregnancy Outcomes:

Preterm infants are babies born before 37 completed weeks of gestation. These usually have lower birth weight ≤ 2500 gm, which increases the perinatal mortality rate significantly. Maternal infections of the genital tract initiate an inflammatory response from the mother by way of the uterus. This can lead to the release of prostaglandins and MMPs (59,60). The link between periodontal disease in the mother and adverse pregnancy outcomes has been observed to be due to the inflammatory response of the bacteria and the host. In fact, bacteremia arising from an active periodontal disease can reach the uterus and expose the maternal-fetal unit to bacteria and bacterial by-products, which cause a preterm birth. (61).

Conclusion:

It seems that there is a strong association between periodontal disease and systemic health. Actually, the relationship between periodontal disease and systemic diseases is in both ways. Systemic diseases can influence the onset of the periodontal disease, and on the other hand presence of periodontitis can exacerbate the systemic health issue. Periodontitis perturbs the oxidant-antioxidant balance, resulting in oxidative stress and the related pathological damage. Such pathological also may contribute to the development of systemic diseases. For instance, periodontitis-related oxidative stress has been known to exacerbate diabetes, cardiovascular disease, and other disorders. Elucidation of the complex interrelationship between periodontitis and systemic diseases would be important in the prevention or management of various systemic conditions. It is envisaged that such studies will unravel new therapeutic approaches, increase awareness of oral hygiene, and introduce new modalities of treatment that reduce the risk of comorbidities associated with periodontitis. The knowledge of this relationship will further result in better health outcomes when interventions are made on both periodontal and systemic health.

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