

## Melatonin: It's Antioxidant Effects on Periodontal Disease

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### Abstract

Melatonin is a hormone that is secreted from the pineal gland in cases where there is no light and is effective in regulating many biological functions such as sleep, circadian rhythm, immunity and reproduction. Melatonin has a free radical scavenger, immunity-supporting and antioxidant effect. Periodontal disease is a common chronic inflammatory disease. This disease has stages ranging from gingivitis to periodontitis. Supportive tissue destruction due to periodontal disease causes tooth loss. Previously, the existence of an inverse relationship between the amount of antioxidants and LPO products has been demonstrated in periodontal disease. PMNL infiltration plays an important role in periodontal disease. These cells produce large amounts of ROS that cause tissue damage. Determination of oxidative stress parameters and melatonin in the individuals with periodontal disease may provide important information on susceptibility to this disease, prognosis and treatment.

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### Introduction

Periodontal disease is a multifactorial disease. Etiopathology and etiopathogenesis of periodontal disease are not clear. However, it is known that the microorganisms in the mouth start a process and attack healthy tissue. The direct effect of bacterial-derived toxic products and the stimulation of the immunological system with bacterial infection results in damage to the periodontal tissue [1].

It is thought that the increase of reactive oxygen and nitrogen species in periodontal disease is responsible for the oxidative damage in periodontal tissues [2]. There is a decrease in the antioxidant defense mechanism with the increase in free radical production. This imbalance between the prooxidant and the antioxidant system may cause further oxidative damage and destruction of periodontal tissue [3].

In addition, neutrophil migration to the gingiva in periodontitis causes abnormal ROS production and exacerbates cardiovascular diseases and other diseases by affecting other organs through circulation [4].

Melatonin has a free radical scavenger, immunity-supporting and antioxidant effect. Melatonin has been shown to be produced in retinas, ovaries, lens, gastrointestinal tract and immun

system cells apart from the pineal gland. Recent research has also shown that melatonin has beneficial effects on bone regeneration and fibroblast activity [5].

### Periodontal Disease

Periodontal disease is a chronic, inflammatory, infectious disease characterized by the destruction of bone and connective tissue caused by dental plaque bacteria and bacterial products [6-8]. Two important types of periodontal disease are gingivitis and periodontitis [9]. Gingivitis refers to the inflammation of the soft tissues surrounding the tooth that develops due to the dental microbial plaque. Metabolic, genetic, environmental and other factors affect gingivitis [10]. Periodontitis is an inflammatory disease characterized by periodontal ligament, alveolar bone and soft tissue destruction [11,12]. Although gingivitis develops before periodontitis, gingivitis does not always pass through periodontitis.

The primary cause of periodontitis is bacterial infection. Several bacterial strains in the dental plaque are known to be associated with periodontitis. The main etiological agent in periodontal disease is gram (-) anaerobic, facultative and virulent bacteria located in the microbial dental plaque in the subgingival area. *P. gingivalis*, *A. actinomycetemcomitans*,

*Prevotella intermedia*, *Bacteroides forsythus*, *Campylobacter rectus*, *Eubacterium nodatum*, *Treponema denticola*, *Fusobacterium nucleatum* are some of these bacteria [13].

### Pathogenesis of periodontal disease

Colonizing microorganisms and their products in the gum formation initiates inflammatory response in periodontal disease. The etiologic factor is gram (-) anaerobic, facultative bacteria in subgingival microbial dental plaque in periodontal disease. However, the host response against microbial products is an important step in this process.

The progression of periodontal disease depends on host response to bacterial and bacterial products. The host response develops as antibodies or cellular reactions against specific bacterial antigens. Depending on these reactions, localization of the event is ensured and a serious systemic infection is prevented.

Bacterial and products induce inflammatory responses in the tissues, resulting in polymorphonuclear leukocyte migration, differentiation into fibroblasts, activation of macrophages and a number of products such as Interleukin-1 (IL-1), Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), prostaglandins and hydrolytic enzymes leading to hard and soft tissue destruction [14,15].

It is thought to be the cause of the destruction of tissues in periodontal disease that bacterial and host interaction, effect of genetic and environmental factors; proteolytic enzymes and inhibitors that play a role in the destruction and repair of cellular and molecular components and the balance between the reactive oxygen species (ROS) and the antioxidant defense system will be degraded [6].

### Periodontitis and oxidative stress

Abnormal plaque response against a specific group of bacteria and their products leads to periodontal tissue destruction. This tissue damage develops directly due to the activation of oxidative stresses, and indirectly the activation of redox-sensitive gene transcription factors such as Nuclear Factor kappa B (NF- $\kappa$ B) and pro-inflammatory cytokine/chemokine production.

This type of host response; characterized by high levels of inflammation associated with excessive proteolytic enzyme and ROS production [16].

When the role of ROS in periodontal disease is assessed; it is thought that oxidation-related changes cause delayed migration of neutrophils into the tissues and that the tissues increase the potential to produce ROS, both of which are considered to be the primary pathogenesis of periodontal disease. The efficacy of ROS is based on the neutrophil infiltration, which is based on the response to bacterial invasion in the pathological breakdown of connective tissue in the periodontal disease process. In this respect, the role of ROS in periodontal disease is important.

Antioxidant enzyme activity was found to be increased in inflamed periodontal tissues in periodontitis [17]. In a study evaluating serum antioxidant levels in the presence of periodontitis, the opposite correlation between the increase in the severity of the disease and the levels of vitamin C, bilirubin and total antioxidant

capacity in serum was determined. The increase in serum antioxidant concentrations, it was suggested that relatively reduce the risk of periodontitis [17].

## Oxidative Stress

### Free radicals/reactive oxygen species

Free radicals are highly active atoms and molecules that can be produced in the physiological and pathological processes that carry one or more unshared electrons in the external orbital. These radicals which are highly unstable, can be found in organic and inorganic form. The presence of unshared electrons in the external orbitals of the molecules increases the reactivity of free radicals. For this reason, free radical is a molecule with high activity [18,19].

Free radicals can be positively or negatively charged or neutral and most often result in electron transfer. The most important free radicals are oxygenated radicals. Oxygen ( $O_2$ ) is the most widely used molecule that easily reaches all the cells. ROS are normally present in organisms under normal conditions [20].

$O_2$  and nitrogen dioxide ( $NO_2$ ) molecules are free radical sources. The most important of the free radicals are oxygen-derived radicals.  $O_2$  is not toxicly active but turns into free oxygen radicals during aerobic cell metabolism. By the reduction of  $O_2$ , the hydroxyl (-OH) radical and superoxide ( $O_2^-$ ) radical are present. Furthermore, singlet oxygen radical ( $^1O_2$ ) and hydrogen peroxide ( $H_2O_2$ ) molecules are known as non-radical ROS [21,22].

## The Effects of Free Radicals on Biological Mechanism

When the existing balance between free radicals and antioxidant defense mechanisms deteriorate in favor of oxidants, free radicals interact with biomolecules such as proteins, carbohydrates, lipids and DNA, causing metabolic changes in the cell [18,19,23,24].

### Antioxidants

Antioxidant defense systems have been developed to limit the levels of ROS and the damage it causes in organisms. Antioxidants inhibit lipid peroxidation (LPO) by inhibiting the peroxidation chain reaction and/or collecting ROS.

Antioxidants can be divided into two major groups, namely endogenous and exogenous antioxidants. It is possible to classify antioxidants in different forms. A classification can be made of those that inhibit the development of the ROS, and those that neutralize existing free radicals. Also a classification can be made of those in the enzyme structure and those not in the enzyme structure [25].

Antioxidant compounds have a very different effect mode and activity level. They reveal one or more of the different forms of action, such as cleaning of ROS and nitrogen species, repair of damaged tissues by oxidative stress, repair/renewal of other antioxidants and metal chelating. An ideal antioxidant can fulfill most of these effects.

The balance between the degradation and the formation of oxidants is important in maintaining biological integrity of cells and tissues in biological systems [26].

## Melatonin

Melatonin (N-acetyl-5-methoxy-tryptamine), secreted from the pineal gland and other organs, is an antioxidant and anti-inflammatory agent. Melatonin, first described in 1917, was not isolated until 1958 [27]. Melatonin was identified by dermatologist Lerner in 1958 [28].

In mammalian, the pineal gland, which can convert photic information into neuroendocrine signals, secretes melatonin in response to visual transmission from the retina [29]. The release of melanocytes during the night leads to a chemical release in the dark area. Light inhibits melatonin synthesis by inhibiting pinealocyte activation [30].

In healthy individuals, the most melatonin synthesis occurs between midnight and 02:00. However, there is minimal production during the day [31].

After melatonin is synthesized in the pineal gland, direct circulation is achieved, reaching the target cells through membrane receptors. Studies have shown the presence of melatonin receptors in various areas of the brain, blood vessels, ovaries, intestines and liver [32,28]. Due to its lipophilic nature, melatonin can easily enter all fractions of the cell [29].

Melatonin has been reported to be related to various biological events such as sleep, emotional state, immunity, thermoregulation, sexual maturation and reproduction, especially the circadian rhythm. In addition, it is thought that melatonin, which has been shown to have antiproliferative and antioxidant effects in studies, may be effective in the treatment of cancer and prevention of aging [32]. Melatonin is one of the strongest antioxidants in comparative studies [33].

In a number of experimental studies, melatonin has been shown to be effective in the treatment of Alzheimer's disease [34], epilepsy [35], infectious and inflammatory diseases [36] and aging [35] have shown beneficial effects in the treatment of physiological processes.

In general, when looking at the antioxidant properties of melatonin, it appears that it has a wide range of effects, including the reduction of the synthesis of proinflammatory cytokines and adhesion molecules [29].

## Melatonin vs. Periodontal health

Melatonin reaches every cell in the organism due to its high lipophilic nature. It is found in high concentrations in the intestines, bone marrow and subcellular organelles such as the

nucleus and mitochondria. Melatonin passes passively from the saliva to the oral cavity after passage to the blood [37].

While the concentration of melatonin is 24% for saliva, this rate is 33% in plasma. Approximately 70% of plasma melatonin binds to albumin, and this melatonin does not cross appreciably into the saliva [38]. Since the melatonin in saliva is not bound to the circulating albumin, it shows the level of free melatonin [39]. A small proportion of the antioxidant potential in the oral cavity is associated with uric acid and less frequently, vit-C and albumin.

The inflammatory process may trigger increased plasma melatonin concentration in periodontitis. This leads to an increase in melatonin in the oral cavity and indicating that plays a protective role. There is a significant increase in melatonin level in elderly patients with excessive periodontal insult. Thus, the increase in melatonin in periodontal disease may be secondary to the increase of free radical products in these pathologies [38].

An increase in salivary melatonin level can affect the periodontal inflammatory process and improve the defensive response of the organism due to the antioxidant and anti-inflammatory effects of melatonin [40-43].

In a study, salivary melatonin levels were reported to vary according to the severity of periodontal disease. The level of periodontal disease increases while the level of salivary melatonin decreases. This suggests that melatonin can protect the body from external bacterial attacks [44].

In addition to the antioxidant properties of melatonin, it supports immunity and increases bone remodeling and proliferation. Release of melatonin to the oral cavity via saliva has been newly described for oral health.

The protective role of melatonin in periodontal tissues can be explained by its antimicrobial properties [45], immunomodulation [46] anti-inflammatory and free radical scavenging effect [47,48].

## Conclusion

Melatonin administration can be used to reduce periodontal disease and elevated oxidative stress levels in these patients. Applied melatonin may protect the oral cavity against ROS injury resulting from inflammatory pathologies and may reduce alveolar bone loss. It is thought that biological mediators such as melatonin may contribute to the protection of periodontal tissues [48,49].

As a result, the disease development capacity of the oral cavity may increase in patients with lower levels of salivary melatonin, especially in elderly individuals or in pathologies characterized by salivary gland malfunction. It may be appropriate to administer melatonin locally or systemically in these patients [44,50].

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