

# Melatonin and Periodontitis -A Review.

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**Abstract:**

The concept of periodontal diseases as localized entities affecting only the teeth and supporting apparatus has been revised in the past few decades with considerable research focused upon the wide ranging systemic effects of these diseases. One of the mechanisms through which systemic health is affected in patients with periodontitis is via generation of reactive oxygen species and oxidative stress which induce a great deal of damage to various body tissues. To address this aspect, use of antioxidants has become a standard part of medicinal treatment. Melatonin, an endogenous hormone produced by pineal gland is a powerful anti-oxidant and possesses a number of other potentially beneficial biologic activities to prevent the damage produced by oxidative stress on periodontium and other organ systems. Current review article provides contemporary evidence for the role of melatonin in periodontal diseases and envisions at the emerging status of melatonin to be utilized as diagnostic, risk reduction and therapeutic strategies in the field of periodontal medicine.

**Keywords:** melatonin, inflammation, oxidative stress, immunological system, oral cavity

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## INTRODUCTION

Periodontitis is a chronic inflammatory disease of the tissue surrounding and supporting the teeth[1].The main initiating factor of these diseases is dental plaque.The presence of microorganisms in the dental plaque initiates a series of processes leading to the damage of healthy tissue[2].Overgrowth of several gram-negative bacteria present in the dental plaque produce several bacterial products leading to an excessive host immune response(3). Activation of the innate and adaptive immunity counteracts the bacterial attack, these causes destruction of the periodontal tissue by secreting high amounts of inflammatory cytokines,proosteoclastogenic factors, and matrix metalloproteinases[4].These damage of periodontal tissues results from a direct effect of the toxic products released by the bacteria, and from the action of the immune system stimulated by the bacterial infection [5]. An important feature in PD is the generation of free radicals, some of which derive from the bacteria themselves, and others originate from the immune response [6]. It is suggested that an increase in both reactive oxygen and nitrogen species during PD is responsible for the oxidative damage to periodontal tissues [7]. Furthermore, periodontal disease is associated with an imbalance in the oxidant/antioxidant systems.

Melatonin is the major secretory product of the pineal gland and is mostly associated with regulation of the circadian dark/light rhythm of the human body [8].It is a free radical scavenger and a broad-spectrum antioxidant.In certain pathologies associated with oxidative stress, melatonin have both anti-inflammatory and bone repair effects.It has immunomodulatory and antioxidant activities, stimulates the proliferation of collagen and osseous tissue and acts as a protector against cellular degeneration associated with aging and toxin exposure. In the oral cavity, particularly the antioxidant function of melatonin suggests its involvement in pathogenic processes of periodontal disease[9].Cyclooxygenase (COX)-2 is the key

enzyme that catalyzes the two sequential steps responsible for biosynthesis of prostaglandins (PGs) from arachidonic acid. The inducible isoform of COX, namely COX-2, plays a critical role in the inflammatory response, and its overexpression has been associated with several types of pathology, it has been shown that melatonin and its metabolites exert a suppressive effect on the activities of COX-2 and inducible nitric oxide synthase (iNOS)[10].Additionally, the metal binding capacity of melatonin inhibits microbial growth in vitro, especially of gram-negative microorganisms, which are mainly related to periodontal disease[11].Hence periodontal therapy of melatonin reduces inflammation of the periodontium and balances the oxidant/antioxidant status.Accordingly objective of this study is to access the role of melatonin as a diagnostic, risk reduction and therapeutic strategies in the field of periodontal medicine.

## MELATONIN AS AN ANTIOXIDANT & FREE RADICAL SCAVENGER:

Periodontal tissue is destroyed in the course of periodontitis by disproportionate immunologic responses to a triggering agent such as bacteria in biofilm (12)Generation of reactive oxygen species from these biofilm is one of the multifactor phenomena affecting periodontitis. ROS are derived from the bacteria themselves and also released as a consequence of the immune response such as secondary polymorphonuclear to infiltration leukocytes.[13]These free radicals generated by the phagocytic cells, e.g., neutrophils and macrophages, migrate to the inflammation site, and significantly damage the gingival tissue.ROS can also interact with nitric oxide (NO), producing various reactive nitrogen species (RNS), including nitrosonium cation (NO+), nitroxyl anion (NO-) and peroxynitrite (ONOO)[14].Lipid peroxidation is a major factor in the induction and progression of chronic periodontitis.The major and important property of melatonin is its ability to serve

as a very potent free radical scavenger. Melatonin has scavenging actions at both physiologic and pharmacologic concentrations. Melatonin and several of its metabolites can detoxify free radicals and their derivatives(15).

#### **Mechanism:**

The imbalance between the pro oxidant and antioxidant systems may lead to a further oxidative attack and substantial deterioration of the periodontal tissues [16]. In response to antigenic stimuli, T lymphocytes produce interleukin-2 (IL-2). IL-2 regulates a series of processes in different cells of the immune system including natural killer cells, monocytes/macrophages and B lymphocytes.(17)

Mechanism by which melatonin detoxifies the OH radical is that indoleamine donates an electron to the radical, thereby eliminating its reactivity. In this process, melatonin itself becomes a radical referred to as the indolyl cation radical,“ which interacts with a second OH to cyclic 3hydroxymelatonin. N1-acetyl-N2-formyl-5methoxykynuramine and N1-acetyl-5methoxykynuramine are additional byan Nacetyltryptamine lacking the 5-methoxy group and possessing a 2-benzyl substitution, has also been reported to be a competitive melatonin antagonist. These metabolites of melatonin because of its high lipophilicity, it crosses cell membranes easily to reach each subcellular compartment, including the mitochondria, where it is found in high concentrations. In addition, melatonin interacts with lipid bilayers and stabilizes mitochondrial inner membranes an effect that may improve ETC activity. (18) The ability of melatonin to influence mitochondrial homeostasis has been tested in in vivo and in vitro experiments. Melatonin reportedly increased the activities of the brain and liver mitochondrial respiratory complexes I and IV in a time-dependent manner after its administration to rats(19). Besides the direct antioxidant effects described above, indirect antioxidant actions of melatonin have been reported. Melatonin can regulate the production of NO through its interaction with the enzymes that synthesise it. In vivo studies indicated that melatonin inhibited mtNOS expression and activity in an experimental model of sepsis in young and old rats. The relative importance of melatonin, in terms of its free-radical scavenging properties and its indirect stimulation of antioxidative enzymes in terms of reducing oxidative stress, remains to be determined. Thus, melatonin is classified as a suicidal or terminal antioxidant(20).

#### **MELATONIN AS A PROMOTER OF BONE FORMATION:**

Melatonin influences fibroblast activity and bone regeneration by promoting osteoblast differentiation and bone formation and additionally, it stimulates the synthesis of type I collagen fibres (21). Melatonin mediates these effects through receptors localised on preosteoblasts, which lead to the production of bone sialoprotein, alkaline phosphatase, osteopontin and osteocalcin in these cells, thus significantly shortening the time needed for their

differentiation into mature osteoblasts from 21 to 12 days .The receptor activation of nuclear factor-kappa B ligand (RANKL) is an important protein in osteoclastic differentiation and proliferation .Another protein, osteoprotegerin (OPG), interferes with its biologic potential. RANKL and OPG plays a critical roles in the development of periodontal disease, with periodontal bone destruction resulting from the upregulation of RANKL and downregulation of OPG. Melatonin alters these events by modulating the molecular triad of OPG/RANK/RANKL (22). Also, treatment with melatonin stimulates the proliferation, differentiation and activity of osteoblasts. Recent studies have demonstrated that a melatonin derivative, i.e., 1-benzyl-2,4, 6-tribromomelatonin, has more potent activity than melatonin itself, and may have potential use in the treatment of bone diseases of the oral cavity as well as osteoporosis (23).

#### **Melatonin- Anti Inflammatory :**

The antioxidant properties of melatonin may be beneficial for the treatment of the local inflammatory lesions and for accelerating the healing process, e.g., after tooth extraction and other surgical procedures in the oral cavity. Favorable effects of local melatonin administration have been observed to the alveolar sockets after molar and premolar extraction in Beagle dogs (24). In the dogs in which melatonin was not used, elevated levels of products of lipid peroxidation and nitrite plus nitrate levels in plasma as well as the GSSG/GSH (oxidized glutathione/reduced glutathione ratio) in erythrocytes were measured. Dogs in which 2 mg melatonin was applied to the vacated socket immediately after extraction did not show these increases (25). Melatonin also has been shown to inhibit the inflammatory enzyme cyclooxygenase-2 (COX-2). Melatonin binds to the active sites of COX-1 and COX-2 indicating that it may act as a natural inhibitor of these enzymes and thereby be an endogenous inhibitor of inflammation. The anti-inflammatory and immunostimulatory actions of melatonin are well known (26).

#### **Melatonin –Therapeutic Agent:**

The amount of salivary melatonin varied according to the severity and extension of periodontal disease: generalised severe chronic periodontitis had the least salivary melatonin level. This finding suggests that melatonin might possess the ability to fight against inflammation, probably due to its antioxidant, anti-aging, and immunoenhancing action. It is well known to be associated with inflammation of periodontium that destroys periodontal ligament and alveolar bone by resorption. These processes mainly involve osteoclasts, which are mediated by cytokines and local factors released by neighboring defensive cells in response to established bacterial aggression(28). Melatonin has a main role in the regulation of proteins implicated as mediators of these processes. The receptor activator of nuclear factor-kappa B ligand (RANKL) is a highly important protein in osteoclastic differentiation and proliferation. Another protein, osteoprotegerin (OPG),

interferes with its biologic potential. It is demonstrated that these proteins play a critical role in the development of periodontal disease, with periodontal bone destruction produced by the upregulation of RANKL and downregulation of OPG(29). Melatonin can modulate these events because it is closely related to orchestration of the molecular triad OPG/RANK/RANKL. Collectively, these protective actions of melatonin may also have potential clinical applicability for individuals with medically compromised states, especially where periodontal surgery is contra-indicated, melatonin administration may improve periodontal status as well as systemic health. Hence it can be used as non surgical treatment as therapeutic agent for periodontitis.(30)

Melatonin may act as a potential risk marker in the saliva of patients with periodontal disease because its levels vary concordantly with periodontal disease and could provide essential information about their susceptibility to this disease and their prognosis. Not only for periodontal disease, its salivary levels can also be risk marker for other systemic diseases showing alteration in melatonin levels; as salivary levels reflect plasma melatonin levels. Further studies have indicated that the amount of salivary melatonin decreases from clinically healthy subjects to subjects with periodontitis.

#### CONCLUSION:

Melatonin have clinical applications in reducing oral diseases; limiting tissue damage that is a result of free radicals, stimulating the immune response, reducing the progressive loss of alveolar bone, promoting the regression of symptoms of impeding local inflammatory lesions, and possible treatment . Melatonin has the following positive aspects: it is endogenously produced, it is non-toxic, it diffuses rapidly into all cells and body fluids, it penetrates all subcellular compartments, it is generally devoid of pro-oxidant actions, and it stimulates a number of antioxidant enzymes. Melatonin released into the oral cavity via the saliva may have yet-to-be-identified benefits for oral health. Individuals as the result of pathologies that are characterized by a malfunction of the salivary glands may have an elevated capacity to develop diseases of the oral cavity. The administration of melatonin, in local or systemic form, might be indicated in these patients, with the goal of protecting their mouth against inflammatory and infectious processes of a diverse nature. On the one hand, melatonin levels might be constantly lower and represent a risk indicator for the development of periodontal disease. On the other hand, melatonin levels might be depleted in response to an increased oxidative stress and the bacterial attack, which are both present in periodontitis. Ability to neutralise reactive species, where it inhibits bone resorption. There is some evidence that topical application of melatonin may act as a biomimetic agent in the periodontal therapy. Clearly, the functional aspects of melatonin in the oral cavity needs additional investigating and may prove to be a fertile area for research. If melatonin has an effect in improving any aspect of oral health, the

regular use of currently-available sublingual tablets may be found to be useful as a means of treatment.

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