Review Article

Role of Melatonin in Periodontal Diseases: A Structured Review

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Abstract

Melatonin is produced by the pineal gland and plays a role in regulating circadian rhythm. It influences the physiologic processes, such as the activation of the immune system and the antioxidant function. Melatonin has been reported in the samples of patients with periodontitis. Therefore, the role of melatonin in periodontal diseases must be appraised. Using the strategy of electronic search of various databases, we included studies, published until December 2021, measuring the expression of melatonin in patient samples and evaluating the effect of periodontal therapy on melatonin expression. This review also included studies evaluating the effect of melatonin supplementation on periodontal parameters. In total, 15 articles fulfilled the study inclusion criteria. The results revealed that melatonin is negatively correlated with the severity of periodontal diseases, and melatonin supplementation reduces the levels of periodontal inflammatory parameters. Hence, melatonin has a role in periodontal diseases, but additional studies are warranted to substantiate its use as a biomarker and host modulatory agent.

Keywords: Antioxidant, biomarker, host modulation, melatonin, periodontitis

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Introduction

Periodontal diseases are chronic inflammatory diseases of the tissues supporting and surrounding the teeth. The prominent causative gram-negative bacteria in the dental plaque trigger the disease process by inducing an excessive host immune response. While counteracting the bacterial attack, this excessive host response leads to the destruction of periodontal tissues by secreting high levels of inflammatory cytokines, pro-osteoclastogenic factors, and matrix metalloproteinases.[1,2] The disease process can lead to the generation of free radicals such as reactive oxygen and nitrogen species during periodontal diseases.[3,4] This increased free radical production further decreases the antioxidant defense. This imbalance between the pro-oxidant and antioxidant systems may further result in oxidative attack and extensive deterioration of periodontal structures.[5,6]

Melatonin is a hormone synthesized and secreted by the pineal gland. This hormone plays a role in physiologic processes such as circadian rhythm control, immune system activation, and body temperature regulation.[7,8] Melatonin also has an antioxidant function as it serves as a direct free radical scavenger, stimulates antioxidative enzyme production and increases its efficiency.[9]

Melatonin levels are significantly decreased in the saliva, serum, and gingival crevicular fluid (GCF) of periodontitis patients compared with healthy controls.[10-13] The antioxidant function of melatonin suggests that this hormone is involved in the pathogenic processes of periodontal diseases.[9] Thus, the role of melatonin in periodontal diseases needs to be assessed.

This structured review evaluates the role of melatonin in periodontal diseases by addressing the following questions:

- What are the levels of melatonin in periodontal health and disease? Is there a change in melatonin levels with increasing severity of the disease?

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- What is the effect of periodontal therapy on melatonin levels?
- Which samples are used to assess melatonin levels?
- What is the role of melatonin in periodontal therapy?

Materials and Methods

Search strategy

To address the aforementioned questions, a comprehensive literature search of the following databases was performed using the keywords melatonin and periodontal diseases. We searched for papers published until December 2021. No limits and language restrictions were applied during the electronic search to obtain all the relevant articles pertaining to the review topic. In addition, a manual search for articles was conducted.

The search strategy is represented in Figure 1.

Databases

1. PUBMED
2. PUBMED CENTRAL
3. MEDLINE
4. SCIENCE DIRECT
5. EMBASE
6. LILAC
7. U.S. NATIONAL LIBRARY OF MEDICINE
8. MeSH
9. GOOGLE SCHOLAR.

Inclusion criteria

Studies associating melatonin levels and different types of periodontal diseases or disease severity were included. Clinical trials assessing melatonin levels and the influence of melatonin on periodontal therapy were also included.

Exclusion criteria

In vitro studies (both human and animal) and case reports were excluded.

Search results

The systematic search in all electronic databases based on the relevance of the title and abstract to the topic of interest returned 26 articles. The search was completed by checking the reference terms and the key words given in the relevant articles. A manual search was also conducted. Full text for the relevant articles fulfilling the inclusion criteria was retrieved. After assessing the full text, 15 articles relevant to this review and satisfying the inclusion criteria were subjected to data extraction.

Data extraction

Data were extracted by two independent review authors. In case of any disagreement on the inclusion of certain articles, a discussion was conducted to resolve it. When a study did not report raw data but included precise graphical representations, the data were extracted. The articles were classified based on the levels of evidence given by the Centre for Evidence-Based Medicine (available online at http://www.cebm.net/).

Results

In total, 15 articles were selected according to the inclusion and exclusion criteria. Table 1 presents the general information regarding the articles. Table 2 presents the level of evidence of the selected articles.

Melatonin levels in periodontal disease

The melatonin concentration was estimated in 13 studies. Nine studies compared melatonin levels in healthy and chronic periodontitis patients.[13-21] Five studies compared melatonin levels in healthy people and patients with chronic periodontitis and gingivitis.[13,16-18,21] Four studies estimated melatonin levels in periodontitis patients, but the type of periodontitis was not specified.[11,12,22,23] Three studies reported melatonin levels in patients with aggressive periodontitis.[15,16,20] Bertl K *et al*.[15]

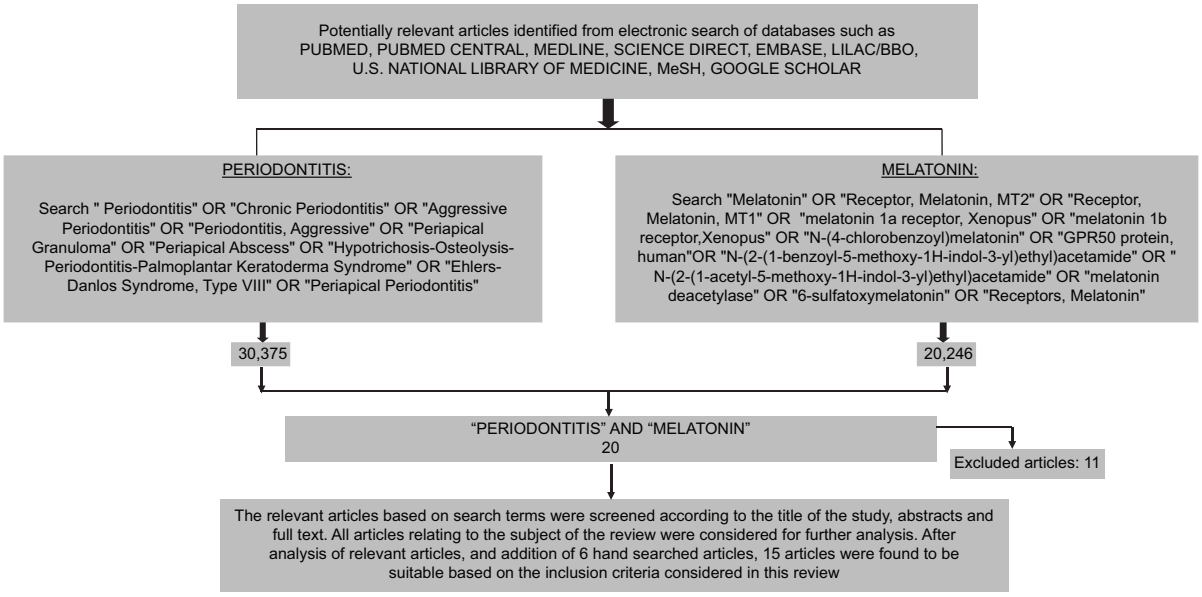

Figure 1: Selection flow chart depicting the selected articles

Table 1: General information of selected articles

Author	Study design	Results
Cutando A *et al*. 2006[10]	Cross sectional study	There is a significant correlation between Community Periodontal Index (CPI) and Salivary/ Plasma melatonin ratios. As the degree of periodontal disease increased, the salivary melatonin level decreased.
Srinath R *et al* 2010[13]	Cross sectional study	Salivary and GCF melatonin levels (mean: 2.17 pg/ml and 1.54 pg/ml respectively) were found to be reduced to lowest concentrations in chronic periodontitis.
Mhaske n *et al* 2010[14]	Cross sectional study	A negative association between the salivary melatonin levels and periodontal severity was seen.
Bertl K *et al* 2013[15]	Longitudinal study	Periodontal therapy resulted in a statistically significant increase of the salivary melatonin levels.
Almughrabi OM *et al* 2013[16]	Cross sectional study	Progressive decreases in the salivary and GCF melatonin levels are seen from health to periodontitis groups.
Bertl K *et al* 2013[15]	Longitudinal study	Significant negative correlation was seen between change in melatonin levels and bleeding on probing after treatment (P=0.02)
Hagh L *et al* 2013[17]	Longitudinal study	The non-surgical treatment significantly increased salivary melatonin levels in severe and moderate periodontitis and gingivitis groups.
Hagh L *et al* 2014[18]	Cross- sectional study	Healthy subjects had a significantly higher salivary melatonin level compared to patients with gingivitis and there is a significant difference between salivary melatonin levels in patients with gingivitis and periodontitis.
Balaji TM *et al*. 2015[19]	Cross- sectional study	There was no significant difference in plasma (P=0.933) and salivary (P=0.266) levels of melatonin in the two groups.
Ghallab NA *et al* 2016[20]	Cross- sectional study	GCF-MDA levels were significantly higher in the GAgP group compared to CP, and higher in CP group compared to the C group.
Lodhi K *et al* 2016[21]	Cross-sectional study	The melatonin levels were positively significant related to gingival index and probing depth.
Bazyar H *et al* 2018[23]	Randomized Controlled Trial	The mean serum levels of melatonin were significantly increased post-intervention (4.52±1.78 and 5.03±1.68 pg/mL, respectively; P=0.005).

Table 2: Level of evidence of selected articles based on the oxford centre for evidence-based medicine – levels of evidence criteria {AVAILABLE ON http://www.cebm.net/}

Author	Study design	Level of evidence
Cutando A *et al*. 2006[11]	Cross sectional study	3b
Gomez-Moreno G. *et al*. 2007[12]	Cross sectional study	3b
Srinath R *et al*. 2010[13]	Cross sectional study	3b
Mhaske N *et al*. 2010[14]	Cross sectional study	3b
Bertl K *et al*. 2012[15]	Longitudinal study	2b
Almughrabi OM *et al*. 2013[16]	Cross sectional study	3b
Bertl K *et al*. 2013[17]	Longitudinal study	2b
Hagh L *et al*. 2013[18]	Longitudinal study	2b
Hagh L *et al*. 2014[19]	Cross- sectional study	3b
Balaji TM *et al*. 2015[20]	Cross- sectional study	3b
Ghallab NA *et al*. 2016[21]	Cross- sectional study	3b
Lodhi K *et al*. 2016[22]	Cross- sectional study	3b
El-Sharkawy H *et al*. 2018[23]	Randomized controlled trial	1b
Bazyar H *et al*. 2018[24]	Randomized controlled trial	1b
Tinto M *et al*. 2018[25]	Randomized controlled trial	1b

included patients with aggressive periodontitis in the study but did not mention any specific group for the aggressive periodontitis patients and specific estimation of melatonin levels for that group. Melatonin levels negatively correlated with the severity of periodontal disease and periodontal parameters and indices in all included studies, except one study,[21] which reported an increase in salivary melatonin levels with increased severity of periodontal diseases, contrary to other reports.[21]

Effect of periodontal therapy on melatonin levels

Four studies evaluating the effects of non-surgical therapy on melatonin levels reported that periodontitis treatment increased melatonin levels in patients.[15,17,22,23] An improvement in clinical parameters negatively correlated with the increase in melatonin levels. In this regard, Bazyar H *et al*.[23] investigated the effect of non-surgical therapy, along with melatonin supplementation, in an intervention group and a placebo group. In that study, the mean serum melatonin levels were significantly higher in the intervention group than in the placebo group.

Samples used for assessment

Saliva samples are most commonly used for estimating melatonin levels.[11,12,16-19,21] GCF samples were used in four studies,[11,13,16,19] while serum samples were used in two studies for analyzing melatonin levels.[15,23] Plasma samples were used for estimating melatonin levels in three studies.[11,12,19] Balaji TM *et al*. used gingival samples for assessing melatonin levels.[19]

Influence of melatonin on periodontal therapy

Three studies reported the influence of melatonin on periodontal therapy.[23-25] These clinical trials reported a significant reduction in inflammatory and periodontal

parameters in the intervention groups compared with the control groups. El-Sharkawy H *et al*. and Bazyar H *et al*. included patients with systemic diseases (primary insomnia and type II diabetes, respectively)[23,24] and suggested that melatonin can be used as a non-surgical and reliable adjunctive therapy for the management of periodontitis.

Discussion

Melatonin in periodontal health and disease

Periodontal tissue destruction is a result of the abnormal response against specific bacterial groups. Activation of oxidative stress and the redox-sensitive gene transcription factors such as nuclear factor kappa B, along with the production of proinflammatory cytokines, causes further periodontal tissue destruction. This host response is characterized by high levels of inflammation and excessive production of proteolytic enzymes and reactive oxygen species (ROS).[26] These oxidation-related changes and increased ROS production with the generation of free radicals cause delayed migration of neutrophils into the tissues, thereby leading to further destruction and metabolic changes.[4,27,28]

Melatonin has a protective role and exhibits a negative association with the severity of periodontal diseases, which can be attributed to its antioxidant and immunomodulatory properties. Melatonin has the unique property of "cascade reaction" wherein it serves as a potent antioxidant and free radical scavenger along with its metabolites, thereby stimulating antioxidant enzymes.[29,30] Along with its antioxidant properties, melatonin reduces the synthesis of proinflammatory cytokines and adhesion molecules, thereby reducing periodontal tissue destruction.[31]

Melatonin secretion peaks between 24:00 h and 02:00 h and is the lowest between 12:00 h and 14:00 h. Melatonin secretion also reduces with ageing.[7] Melatonin was found in all the samples assessed, with saliva samples being the most common. The GCG revealed a 60% reduction in melatonin levels compared with serum melatonin levels.[13,32] Salivary melatonin levels do not reflect the absolute serum concentrations as only the free melatonin fraction diffuses passively into the saliva.[33] Moreover, 24%–33% of plasma melatonin passes into the mouth via salivary glands, while the remaining 70% is bound to albumin and remains in circulation.[34] TM Balaji *et al*. found melatonin levels in gingival tissue samples, which could be attributable to the release of melatonin from gingival mast cells or its diffusion into the gingiva from systemic circulation.[19,35] These observations should be further validated to elucidate the mechanism of melatonin synthesis and its presence in gingival tissues.

Of all the studies included in this review, only one exhibited a contradictory result where the salivary melatonin levels increased from healthy to gingivitis to periodontitis groups.[21] The authors suggest that this increase was due to an increase in signals owing to the increased severity of periodontal inflammation in the oral cavity, thereby causing an increased protective response.[21,36,37]

Melatonin as a host modulatory agent in periodontal therapy

Various studies have evaluated melatonin as a host modulatory agent for periodontal therapy. El-Sharkawy H *et al*., Bazyar H *et al*., and Tinto M *et al*. presented the benefits of melatonin supplementation on periodontal parameters and reduction of inflammatory markers, thereby offering evidence supporting the benefits of melatonin use as adjunctive therapy for non-surgical periodontal treatment.[23-25]

Melatonin also possesses antimicrobial properties against certain groups of bacteria and viruses.[38,39] Zhou W *et al*.[40] evaluated the effects of melatonin against *Porphyromonas gingivalis* and found that melatonin could inhibit biofilm formation, in addition to acting on the lipopolysaccharide, thereby decreasing the viability of *P. gingivalis*.

Melatonin has immunomodulatory, antioxidant, and anti-inflammatory properties and has been shown to promote osteoblast proliferation, thereby enhancing bone formation.[41-43] The use of calcium aluminum scaffolds containing melatonin and platelet-rich plasma had a proliferative effect on human osteoblasts, thereby offering avenues in guided tissue regeneration applications.[44]

Reports have suggested the use of melatonin for implant therapy. *In vitro* studies have evaluated the use of melatonin in implant sites and its use along with growth factors around implants to improve the osteogenic effects of bone grafts and osseointegration of implants.[45-47] Clinical trials have also reported that using melatonin for osseointegration of dental implants is beneficial.[48] These investigations warrant further studies to validate the role of melatonin in periodontal and implant therapy.

Conclusions

This structured review shows that melatonin plays a role in periodontal disease, and the conclusions are as follows:

- Melatonin levels negatively correlated with the severity of periodontal disease and periodontal parameters and indices in all the included studies, except one.
- Melatonin levels increased following non-surgical periodontal therapy.
- Saliva was the most commonly assessed sample for melatonin levels. Other samples included GCF, serum, plasma, and gingival tissue samples.
- Melatonin supplementation had a beneficial effect on periodontal parameters, and it reduced the level of proinflammatory markers.

Evidence shows that melatonin can be used as a marker for periodontitis and a host modulation agent in periodontal therapy. However, additional interventional and longitudinal studies are needed to verify its suitability as a marker or treatment modality.

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Conflicts of interest
There are no conflicts of interest.

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