Review Article

Melatonin as an Index of Periodontal Disease

Rocco Franco, Patrizio Bollero[1]

Departments of Biomedicine and Prevention and [1]Systems Medicine, University of Rome "Tor Vergata", Roma, Italy

Abstract

Periodontal disease affects the supporting tissues of the tooth. The clinical manifestation varies from gingivitis to periodontitis. Periodontal disease is triggered by bacterial infection that releases toxins. The imbalance between oxidants and antioxidants determines the progression of periodontal disease. Melatonin (MEL) (N-acetyl-5-methoxytryptamine) is a hormone in the human body. Its production takes place in various organs including the retina, gastrointestinal tract, bone marrow, leukocytes, lymphocytes, skin, and principally pineal gland. Its main function is the regulation of circadian and seasonal rhythm, body weight, reproduction, bone metabolism, and tumor growth. An important function of melatonin is the ability to reduce oxidative stress. The aim of this work is to explain if there are differences in salivary melatonin concentration between periodontal and healthy individuals. The study was conducted utilizing the main scientific databases (PubMed, MEDLINE, and Web of Science). The time window considered for the electronic search was from March 1, 2007, to March 1, 2020. The work takes into account 6 works on the disease. Other studies were excluded as they did not meet the inclusion criteria. Studies revealed a concentration of salivary melatonin compared to patients with periodontal disease. Studies agree that the concentration of melatonin is lower in people with periodontal disease. Only one study showed no difference in concentration. Melatonin, therefore, has a protective effect on the periodontium thanks to its antioxidant properties. The salivary measurement of melatonin could be a useful tool for early detection. It can also be used as a therapy to improve the symptoms of periodontal disease.

Keywords: Free radical, melatonin, periodontal disease

Introduction

Periodontal disease affects the supporting tissues of the tooth. The clinical manifestation varies from gingivitis to periodontitis. Periodontal disease is triggered by bacterial infection that releases toxins. All these facts cause the destruction of the periodontium. The host's excessive immune response also causes a number of reactions which cause the tooth loss. The etiopathogenesis and pathophysiology of periodontal disease are not yet fully understood.[1] Dental plaque bacteria are the main cause; however, the host's response to the pathogen also induces the production of inflammatory molecules, including cytokines and prostanoids, which cause the destruction and progression of periodontal disease. Furthermore, the presence of an imbalance between pro-oxidant enzymes and oxidant enzymes determines the progression of periodontal disease. The presence of reactive species of oxygen causes the destruction of the periodontium. Inflammatory mediators cause an irreversible degradation of connective and bone tissues and the consequent loss of periodontal attachment.[2] Melatonin (MEL) (N-acetyl-5-methoxytryptamine) is a hormone in the human body. Its production takes place in various organs including the retina, gastrointestinal tract, bone marrow, leukocytes, lymphocytes, and skin. However, the production of this hormone occurs largely in the pineal gland, where it is synthesized according to circadian rhythms. The peak of production occurs during the night.[3] Melatonin synthesis occurs through a series of complex reactions. The circadian production of the hormone takes place through the transmission of light-dark information to the pineal gland thanks to the retinohypothalamic and suprachiasmatic tracts. The receptors of this hormone are located in different organs; therefore, it regulates important physiological and pathological processes.[4]

Access this article online

Quick Response Code:

Website: www.ejgd.org

DOI: 10.4103/ejgd.ejgd_72_20

Address for correspondence: Dr. Rocco Franco, Department of Biomedicine and Prevention, University of Rome "Tor Vergata", Via Montpellier, 1, 00133 Rome, Italy. Dental Clinic, University Hospital of Rome "Tor Vergata", Viale Oxford, 81, Rome, Italy.
E-mail: rocco.franco@ptvonline.it

How to cite this article: Franco R, Bollero P. Melatonin as an index of periodontal disease. Eur J Gen Dent 2020;9:103-7.

Submitted: 15-Mar-2020 **Revised:** 20-Apr-2020
Accepted: 08-Jun-2020 **Published:** 15-Sep-2020

Its main function is the regulation of the circadian and seasonal rhythm, body weight, reproduction, bone metabolism, and tumor growth. An important function of melatonin is the ability to reduce oxidative stress. It acts directly through the elimination of reactive oxygen species (ROS). It also acts indirectly through the activation of antioxidant enzymes and blocking the action of pro-oxidant enzymes.[5] Therefore, high levels of melatonin in mitochondria are also evident thanks to its antioxidant and antiapoptotic properties. Antiapoptotic abilities are attributed thanks to the ability of melatonin to activate DNA repair enzymes. The salivary concentration of melatonin varies between one-third and one-quarter of the blood concentration and varies from 1 to 5 pg/ml during the day to 50 pg/ml after the midnight peak. Melatonin is a lipophilic molecule, and it circulates in part linked to albumin and in part free. the free part of melatonin circulates in the blood and enters the major salivary glands, being a lipophilic molecule.[6] The aim of the work is to carry out a systematic review of the literature regarding the concentration of melatonin in saliva, especially in periodontopathic people. Specifically, if there are differences in concentration between periodontal and healthy individuals, the assessment of melatonin concentration can help in the diagnosis and therapy of this pathology.

Materials and Methods

The study was conducted utilizing the main scientific databases (PubMed, MEDLINE, and Web of Science). The time window considered for the electronic search was from March 1, 2007, to March 1, 2020. The term "melatonin" was first combined with "periodontal disease" and then independently with "salivary concentration" using the connector "AND." The web search was assisted using the Medical Subject Headings. The criteria for this review are described in the PRISMA flow diagram. The purpose of this review is to answer the following questions using a PICO method (P: Patient problem/population; I: Intervention; C: Comparison; and O: Outcome):

1. Are melatonin levels lower in periodontitis patients than in the healthy population?
2. Can the concentration of melatonin help in the diagnosis of periodontitis and can it help in improving the progression of the disease?

The following inclusion criteria were used: articles in English, human studies, and clinical trials. Two independent reviewers performed the search, using the same keywords. The risk of bias in this phase is solved by an independent author who conducts the same search. The reviewers excluded the duplicated article, review and animal study. The articles found in this phase are 50. Fifteen articles are excluded because they are duplicates and they do not respect the topic proposed in this review.

The phase of eligibility is conducted by other two reviewers. These authors compare the article founding and select the article that asked the PICO. Articles which did not contain data regarding periodontal disease, melatonin, and salivary are excluded. The authors read all the abstracts and excluded those that do not meet the inclusion criteria. 26 items were excluded at this stage.

In this phase, the risk of bias is solved by an independent author, completely external and unknown to the authors. The number of articles remaining in this phase is 9. Three articles are excluded because they did not use the periodontal index and treat only of oral health.

The synthesis of data is carried out by the authors. All data were extracted. The Author reads the full text of the articles. All the reviewers extract the data regarding the periodontal health, melatonin, and salivary concentration. Articles which not contain the data and the previous keywords were excluded. All doubts, regarding the included articles, are solved contacting the author [Table 1].

Results

Two independent scientists searched the previously mentioned keywords, read the titles, and summarized the abstracts of articles. During an initial reading, they excluded the articles that did not respect the topic. Therefore, articles that responded to the key characteristics were selected. These remaining articles were read, and there of them were excluded because it did not conform to the inclusion criteria established. The complete text of the six remaining articles was read, and all were found to respect the inclusion criteria. In conclusion, six articles were included in the present review. The scientists extrapolated the following data: periodontal index, number of patients, mean age, sex, salivary melatonin concentration, blood melatonin concentration, and melatonin crevicular concentration. Data comparing the concentration of melatonin between patients with periodontal disease and healthy controls were taken into account and extrapolated. The study of Almuragbi *et al*. examines a total of seventy patients. The aim of the work is to measure the amount of melatonin in the crevicular fluid and saliva between patients affected by periodontal disease and healthy controls. They were divided into four groups: twenty patients with good periodontal health, twenty patients with gingivitis, twenty patients with chronic periodontitis, and twenty patients with aggressive periodontitis. Melatonin concentration was assessed with an enzyme-linked immunosorbent assay (ELISA). The data were analyzed statistically via SPSS. An analysis of variance (ANOVA) test was carried out to be able to compare the samples. An alpha level of 0.05 was used to indicate statistical significance

Table 1: Flowchart of the review process

Identification of articles	Papers identified through principal database (PubMed, MEDLINE, and Web of Science) $n=50$
Screening time	After an initial read of titles and abstract (n=35)
Eligibility	A full-text reading and a check of inclusion or exclusion criteria (n=9)
Included	Studies included (n=6)

($P < 0.05$). The results show lower melatonin levels in both gingival crevicular fluid and saliva lower in patients with chronic periodontitis (10.4 and 12.8 pg/mL, respectively) and aggressive periodontitis (8.4 and 8.8 pg/mL) compared to patients with gingivitis (13.9 and 17.6 pg/mL) and in healthy controls (16.6 and 22.9 pg/mL). In conclusion, the results show a higher concentration of melatonin in healthy controls compared to the other groups.[7] The study of Ghallab *et al*. examines the presence of melatonin, malondialdehyde (MDA) in the crevicular fluid of patients with chronic and aggressive periodontitis. The study assessed the concentration of these oxidative markers in the crevicular fluid. The author wants to demonstrate that these markers can be used for the evaluation of oxidative status. Sixty-five people were enrolled in this study. The patients were divided as follows: 15 healthy individuals, 25 with chronic periodontitis, and 25 aggressive periodontitis patients. The author examined plaque index, gingival index, pocket depth, and clinical attachment in the different groups, and finally, gingival crevicular fluid (GCF) samples were extracted. The levels of oxidative biomarkers and melatonin were determined with ELISA. Numerical data were presented as mean and standard deviation (SD) values. One-way ANOVA was used to compare between mean probing depth and clinical attachment level in the three groups. Spearman's correlation coefficient was used to determine the statistically significant correlation between clinical parameters and biomarkers levels. The significance level was set at $P \leq 0.05$. Statistical analysis was performed with SPSS. The results showed significantly higher MDA levels in the group of patients suffering from aggressive periodontitis compared to those suffering from chronic periodontitis. The patients with chronic periodontitis have even higher concentration of MDA compared to the control group ($P < 0.001$). The concentration of melatonin and superoxide dismutase (SOD) is significantly higher in the control group than in the remaining groups ($P < 0.05$). However, the group of patients with aggressive periodontitis showed a lower concentration than the group of patients with chronic periodontitis. The CP group demonstrated a significant negative correlation between MDA and melatonin concentrations.[8]

The study of Gomes-Moreno analyzed blood and salivary levels of melatonin in a healthy population and in people suffering from periodontal disease. The study evaluated a population of 46 of patients with periodontal disease and a group of 26 healthy people. Periodontal health was assessed in all patients using the community periodontal index (CPI). The blood's melatonin concentration and salivary were assessed using radioimmunoassays. Quantitative variables were expressed as mean ± SD, whereas absolute and relative frequencies were calculated for qualitative variables. The Mann–Whitney U-test was used to correlate quantitatively with qualitative variables, and the Student's *t*-test was applied to compare the means of quantitative variables. The Spearman correlation coefficient was used to correlate quantitative and qualitative variables. Melatonin levels in blood (9.46 ± 3.18 pg/mL) and saliva (2.55 ± 0.99 pg/mL) were lower in patients with periodontal disease ($P < 0.001$) compared to healthy control patients (14.33 ± 4.05 and 4.22 ± 0.87 pg/mL, respectively). Melatonin levels are inversely proportional with the periodontal indices. A higher plasmatic melatonin level was noted in patients with advanced periodontal disease (CPI 3–4) than in patients with mild periodontal disease (CPI 1–2). The same goes for salivary melatonin.[9]

The study of Balaji *et al*. assessed the concentration of melatonin in plasma, blood, and gingival tissue. Five patients with periodontal health and 15 with periodontitis were enrolled in the study. Saliva and blood were collected to calculate the hormone value using radioimmunoassay. Gingival tissue samples were collected by excision using a surgical Bard-Parker blade. The nonparametric Mann–Whitney U-test was used to compare the melatonin levels in plasma, saliva, and gingival tissue homogenates between healthy individuals and chronic periodontitis patients. In this statistical tool, the probability value ($P < 0.05$) was considered statistically significant. The results did not show a significant difference in the melatonin concentration between the two groups ($P = 0.266$) ($P = 0.933$). However, the concentration of melatonin in the gingival tissues is lower in patients with chronic periodontal disease than in the control group ($P = 0.015$).[10] The study of Cutando *et al*. examined salivary concentration in patients with periodontal disease. The author mainly examined changes in salivary melatonin concentration, based on the severity of periodontal disease, using CPI. Thirty-six patients with periodontal disease were enrolled. Each of them was analyzed for CPI and blood and salivary concentration of melatonin. The Spearman correlation coefficient was used to analyze relationships among variables. Statistical analysis revealed a correlation between salivary melatonin concentration and periodontal disease severity. A negative correlation was noted between salivary concentration and periodontal disease severity ($P < 0.05$).[11] The study of Srinath *et al*. assessed the concentration of melatonin in saliva and crevicular fluid. Forty-five patients were enrolled in the study. The patients were divided according to the periodontal status into three groups. The first group consists of 15 healthy patients, the second of 15 patients with gingivitis, and the third of patients with periodontal disease. Melatonin levels were calculated using an ELISA. The paired-sample test was used to correlate between saliva and GCF. The concentration of melatonin in the crevicular fluid is significantly lower than the concentration present in saliva (average: 1.54 pg/ml and 2.17 pg/ml, respectively). Lower melatonin concentrations were found in patients with chronic periodontitis compared to those with gingivitis and healthy ones (salivary melatonin: 0.07 pg/ml; melatonin GCF: 0.06 pg/ml; $P < 0.05$).[12]

Conclusion

Periodontal disease has a multifactorial etiology. The main stimulus for progression is the bacterial presence. Periodontal

bacteria release toxic products that cause direct damage. They are also responsible for an immune response from the host who also participates in the destruction of the periodontium. The presence of free radicals leads to an imbalance and triggers molecular processes that lead to the progression of periodontal disease. Furthermore, the presence of bacteria produces a higher production of pro-inflammatory mediators. One of these inflammatory mediators is the cyclooxygenase. Its function is to produce prostaglandin E2 (PGE2) involved in periodontal disease. Furthermore, PG production is caused by interleukin-1β (IL-1β) and IL-6 through cyclooxygenase-2 in human gingival fibroblasts.[13] To confirm this, high levels of PGE2 were found in the gingiva and in the gingival crevicular fluid in periodontal patients. The following pro-inflammatory mediators including Il-6, IL-1β, and PGE2 are the molecular agents that cause alveolar bone resorption. Causal periodontal therapy, therefore, causes a significant reduction in the levels of these cytokines. The cellular and molecular signaling mechanisms leading to the synthesis of these pro-inflammatory cytokines in gingival fibroblasts are mitogen-activated protein kinase, activator protein-1, and nuclear factor-κB. In fact, the inhibition of the previous molecular pathways could block the progression of periodontal disease. IL-1β causes hypoexpression of IL-10, which is an anti-inflammatory cytokine, by periodontal ligament cells.[14,15] This amplifies the process of destruction of periodontal tissues. Periodontal ligament cells stimulated by inflammatory cytokines can cause bone resorption via RANKL. IL-6 is a pro-inflammatory cytokine that regulates the host's response against infections. IL-6 is produced by many individual cells including monocytes, fibroblasts, osteoblasts, and vascular endothelial cells. In addition to the damage mediated by cytokines, there is damage to the tissues due to an imbalance of the oxidizing/antioxidant systems.[16] Therefore, the purpose of periodontal support therapies is to reduce the bacterial concentration, reduce the concentration of inflammatory cytokines, and balance the balance between oxidants and antioxidants.[17] The free oxygen radicals have a very short half-life, and for this reason it is very difficult to measure the presence and quantity. Therefore, a useful evaluation method is the final detection of lipid peroxidation products such as MDA. Thus, this molecule can be used as a marker of oxidative stress. In contrast, there are enzymes that fight oxidation, including SOD. SOD eliminates oxygen radicals (superoxide and peroxide).[18] Studies on periodontal ligament fibroblast enzyme have shown a high presence of SOD; therefore, it can be assumed that SOD is a defense mechanism against oxidative stress. Akalin *et al*., however, showed that SOD has extremely low activity in extracellular fluids, and therefore, its activity in the gingival crevicular fluid is questioned. Melatonin is an indoleamine and is produced by various body glands including mainly the pineal gland.[19] Melatonin has been of particular importance for its antioxidant, antiaging, anti-inflammatory, and immune system improvement properties. Therefore, melatonin performs a dual function on the periodontium. Melatonin has an antioxidant effect on free radicals and has an effect on the immune system. In addition, melatonin modulates functioning on proteins that regulate bone resorption. It inhibits bone resorption and promotes the differentiation of osteoblastic cells in the bone marrow. The oxidative change of the environment could activate nuclear factor-κB. This signaling pathway leads to an increased production of inflammatory cytokines that trigger the destruction of the periodontium. All the studies taken into consideration in this review state that there is a lower concentration of melatonin in patients with periodontitis in both saliva and crevicular fluid. The explanation for the decrease in melatonin could be due to the presence of the toxic metabolite, 5-aminolevulinic acid. It is a compound that creates free radicals.[20] Thus, high levels of oxidants lead to the degradation of melatonin, blocking its antioxidant efficacy. The study of Cutando contrarily showed that melatonin levels increase directly proportional to the severity of periodontal disease and, in fact, at the same time increase the quantity of CD4+ lymphocytes. This event is due to the fact that melatonin in response to inflammation increases and through molecular mechanisms stimulates the production of lymphocytes. However, the concentration still remains lower than in healthy patients.[11] Only the study by Balaji *et al*. found no differences in melatonin between periodontally healthy and sick individuals. All of these can be explained by the fact that melatonin concentration is influenced by many factors including circadian rhythm, systemic antioxidant status, and the sleep–wake cycle. However, the author has found lower melatonin levels in the gingival tissue of patients suffering from periodontitis compared to that of healthy people.[10] Therefore, melatonin certainly has an antioxidant role in periodontal tissues and contributes to their health. In fact, periodontal disease is triggered not only by bacterial toxins but also by an oxidative imbalance. In fact, melatonin could be used both in the early diagnosis of periodontal disease through salivary dosage. In the future, it could be used as a pharmacological therapy for periodontal disease.

Acknowledgment

I thank Prof. Tiberti for help in the data collection.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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