

REDUCED SALIVARY MELATONIN LEVELS IN PERIODONTITIS: INSIGHTS INTO INFLAMMATION AND OXIDATIVE STRESS

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ABSTRACT

Objective: The objective of this narrative literature review is to address the possible correlation with low levels of salivary melatonin as a factor that promotes the development of periodontal diseases.

Methodology: Because this is a narrative literature review, it was necessary to search online databases to obtain a set of articles that could be used in the review. Thus, searches were conducted in the following databases: Cochrane Library, PubMed, EMBASE, and Google Scholar, using the following descriptors: Melatonin, Salivary, and Periodontitis. PubMed searches also included the use of Boolean terms such as "AND" and "OR." These searches yielded a wide range of results, necessitating a study screening process. The screening process was divided into three stages: The first involved deduplication of duplicate articles using Zotero, eliminating duplicates. The second stage involved eliminating articles by reading their abstracts and titles. This phase involved reading both components of the articles, removing studies that were not compatible with the present topic. The third and final phase involved reading the article in its entirety, eliminating articles that did not fit the topic and saving those that did for use in this narrative literature review.

Results: Randomized clinical trials and other studies have shown that people with periodontal disease have lower salivary melatonin levels compared to healthy individuals. Furthermore, other studies have shown that people with type 2 diabetes mellitus and periodontal disease also have low salivary melatonin levels.

Conclusion: Studies have demonstrated a relationship between low salivary melatonin levels in individuals with periodontal disease, however, further randomized clinical trials are needed to further study this relationship.

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Keywords: Melatonin. Salivary. Periodontitis.

NÍVEIS REDUZIDOS DE MELATONINA SALIVAR NA PERIODONTITE: INSIGHTS SOBRE INFLAMAÇÃO E ESTRESSE OXIDATIVO

RESUMO

Objetivo: O objetivo desta revisão narrativa da literatura é abordar a possível correlação com baixos níveis de melatonina salivar como um fator que promove o desenvolvimento de doenças periodontais.

Metodologia: Por se tratar de uma revisão narrativa da literatura, foi necessário realizar buscas em bases de dados online para obter um conjunto de artigos que pudessem ser utilizados na revisão. Assim, foram realizadas buscas nas seguintes bases de dados: Cochrane Library, PubMed, EMBASE e Google Acadêmico, utilizando os seguintes descritores: Melatonina, Salivar e Periodontite. As buscas no PubMed também incluíram o uso de termos booleanos como "AND" e "OR". Essas buscas geraram uma ampla gama de resultados, necessitando de um processo de triagem de estudos. O processo de triagem foi dividido em três etapas: a primeira envolveu a deduplicação de artigos duplicados usando o Zotero, eliminando os duplicados. A segunda etapa envolveu a eliminação dos artigos por meio da leitura de seus resumos e títulos. Essa fase envolveu a leitura de ambos os componentes dos artigos, removendo os estudos que não eram compatíveis com o tema em questão. A terceira e última fase envolveu a leitura do artigo na íntegra, eliminando artigos que não se encaixavam no tópico e salvando aqueles que se encaixavam para uso nesta revisão narrativa da literatura.

Resultados: Ensaios clínicos randomizados e outros estudos mostraram que pessoas com doença periodontal têm níveis mais baixos de melatonina salivar em comparação com indivíduos saudáveis. Além disso, outros estudos mostraram que pessoas com diabetes mellitus tipo 2 e doença periodontal também têm baixos níveis de melatonina salivar.

Conclusão: Estudos demonstraram uma relação entre baixos níveis de melatonina salivar em indivíduos com doença periodontal, no entanto, mais ensaios clínicos randomizados são necessários para estudar mais profundamente essa relação.

Palavras-chave: Melatonina. Salivary. Periodontitis.

NIVELES REDUCIDOS DE MELATONINA SALIVAR EN PERIODONTITIS: INFORMACIÓN SOBRE LA INFLAMACIÓN Y EL ESTRÉS OXIDATIVO

RESUMEN

Objetivo: El objetivo de esta revisión narrativa de la literatura es abordar la posible correlación entre los bajos niveles de melatonina salival y su papel como factor que promueve el desarrollo de enfermedades periodontales.

Metodología: Al tratarse de una revisión narrativa de la literatura, fue necesario buscar en bases de datos en línea para obtener un conjunto de artículos que pudieran utilizarse en la revisión. Por lo tanto, se realizaron búsquedas en las siguientes bases de datos: Biblioteca Cochrane, PubMed, EMBASE y Google Académico, utilizando los siguientes descriptores: Melatonina, Salivar y Periodontitis. Las búsquedas en PubMed también incluyeron el uso de términos booleanos como "AND" y "OR". Estas búsquedas arrojaron una amplia gama de resultados, lo que requirió un proceso de cribado de estudios. El proceso de cribado se dividió en tres etapas: la primera consistió en la deduplicación de artículos duplicados mediante Zotero, eliminando los duplicados. La segunda etapa consistió en la eliminación

de artículos mediante la lectura de sus resúmenes y títulos. Esta fase implicó la lectura de ambos componentes de los artículos, eliminando los estudios que no eran compatibles con el tema en cuestión. La tercera y última fase consistió en la lectura completa del artículo, eliminando los artículos que no se ajustaban al tema y conservando los que sí lo hacían para su uso en esta revisión narrativa de la literatura.

Resultados: Ensayos clínicos aleatorizados y otros estudios han demostrado que las personas con enfermedad periodontal presentan niveles más bajos de melatonina salival en comparación con las personas sanas. Además, otros estudios han demostrado que las personas con diabetes mellitus tipo 2 y enfermedad periodontal también presentan niveles bajos de melatonina salival.

Conclusión: Diversos estudios han demostrado una relación entre los niveles bajos de melatonina salival en personas con enfermedad periodontal; sin embargo, se necesitan más ensayos clínicos aleatorizados para estudiar esta relación con mayor profundidad.

Palabras clave: Melatonina. Salival. Periodontitis.

1 INTRODUCTION

Periodontal disease is a chronic inflammatory condition that affects the supporting structures of the teeth, including the gingiva, periodontal ligament, and alveolar bone. It is primarily triggered by the host's immune response to dysbiotic oral microbiota and is influenced by systemic conditions such as diabetes mellitus, smoking, and oxidative stress. The disease progression involves the release of pro-inflammatory cytokines and proteolytic enzymes, leading to tissue destruction and bone loss (Kinane et al., 2017; Hajishengallis, 2015). In addition to local tissue damage, periodontitis has been linked to systemic inflammatory conditions, highlighting its relevance as a potential risk factor for chronic diseases such as cardiovascular disease and diabetes.

Melatonin, a hormone primarily secreted by the pineal gland, is well known for its role in regulating circadian rhythms. Beyond this, melatonin also exhibits potent anti-inflammatory, antioxidant, and immunomodulatory properties (Hardeland, 2018; Reiter et al., 2014). Importantly, melatonin is also synthesized locally in extrapineal sites, including the oral cavity, where it acts as a free radical scavenger and modulates inflammatory responses (Cutando et al., 2007). These biological activities suggest a potential role for melatonin in the maintenance of periodontal health.

Recent evidence suggests an association between reduced salivary melatonin levels and periodontitis. Studies have shown that patients with periodontal disease exhibit significantly lower levels of melatonin in saliva compared to healthy individuals (Srinath et al., 2010; Cutando et al., 2007). Moreover, randomized clinical trials have demonstrated that adjunctive melatonin therapy, when combined with non-surgical periodontal treatment, improves clinical outcomes such as probing depth reduction and clinical attachment level gain (Bazyar et al., 2021; Anton et al., 2022). These findings point to a potential bidirectional relationship, where periodontal inflammation may suppress melatonin production, and melatonin deficiency may exacerbate oxidative stress and tissue destruction. The objective of this narrative literature review is to address the possible correlation with low levels of salivary melatonin as a factor that promotes the development of periodontal diseases.

2 METHODOLOGY

Because this is a narrative literature review, it was necessary to search online databases to obtain a set of articles that could be used in the review. Thus, searches were conducted in the following databases: Cochrane Library, PubMed, EMBASE, and Google Scholar, using the following descriptors: Melatonin, Salivary, and Periodontitis. PubMed searches also included the use of Boolean terms such as "AND" and "OR." These searches yielded a wide range of results, necessitating a study screening process. The screening process was divided into three stages: The first involved

deduplication of duplicate articles using Zotero, eliminating duplicates. The second stage involved eliminating articles by reading their abstracts and titles. This phase involved reading both components of the articles, removing studies that were not compatible with the present topic. The third and final phase involved reading the article in its entirety, eliminating articles that did not fit the topic and saving those that did for use in this narrative literature review. Furthermore, Rother's (2007) study was used as a guide throughout the development of this article, as it addresses the differences between systematic and narrative reviews, including their approach, structure, methodology, and standards.

3 RESULTS

Several studies indicate that salivary melatonin levels are significantly reduced in patients with periodontitis, supporting the hypothesis that melatonin plays an important role in modulating oral inflammation. A case-control study conducted by Srinath et al. (2010) demonstrated a progressive reduction in salivary melatonin levels as the severity of periodontal disease increased. Healthy individuals had mean melatonin levels of 3.73 ± 1.05 pg/mL, while patients with gingivitis showed 2.45 ± 0.77 pg/mL, and patients with periodontitis had the lowest levels, averaging 1.31 ± 0.56 pg/mL.

In a more recent study by AlGhamdi et al. (2023), salivary melatonin levels were significantly lower in individuals with chronic periodontitis (2.14 ± 0.98 pg/mL) compared to the healthy control group (4.83 ± 1.57 pg/mL). Furthermore, melatonin levels were inversely correlated with probing depth ($r = -0.52$) and plaque index ($r = -0.47$), suggesting that reduced melatonin may be directly associated with periodontal inflammatory activity.

Kara et al. (2019) performed a biochemical evaluation of oxidative and inflammatory biomarkers in patients with periodontitis. The study demonstrated that salivary melatonin levels were significantly lower in the group with periodontal disease (1.15 ± 0.43 pg/mL) compared to the control group (3.92 ± 0.88 pg/mL). Furthermore, there was a significant negative correlation between melatonin levels and malondialdehyde (MDA) levels, a marker of oxidative stress, reinforcing the hypothesis that melatonin deficiency may contribute to the redox imbalance observed in periodontitis.

Another important study by Kozłowska et al. (2022) investigated melatonin expression in gingival fluid and its relationship with the gingival inflammatory index. The results showed that patients with periodontitis had significantly lower melatonin levels in their gingival fluid (mean 12.7 ± 3.1 pg/mL) than healthy individuals (25.4 ± 4.6 pg/mL), with $p < 0.01$. There was also a significant increase in the levels of pro-inflammatory cytokines such as IL-6 and TNF- α in the periodontitis group, which correlated inversely with melatonin.

Finally, interventional studies such as that by Bazyar et al. (2021) showed that the administration of oral melatonin (3 mg/day for 8 weeks) in patients with type 2 diabetes and periodontitis not only improved periodontal clinical parameters (reduction in probing depth and gain in clinical attachment level), but also resulted in a significant increase in salivary melatonin levels compared to the placebo group ($p < 0.05$), suggesting a therapeutic potential of melatonin in modulating the periodontal microenvironment.

4 DISCUSSION

The analysis of the selected studies reinforces the hypothesis that reduced salivary melatonin levels are associated with the development and progression of periodontitis. Melatonin plays a protective role in the oral cavity through its antioxidant and anti-inflammatory properties, neutralizing free radicals and regulating the local immune response. Its deficiency may, therefore, favor the perpetuation of the inflammatory cycle and tissue damage characteristic of periodontal disease.

In addition to being a potential marker of disease activity, melatonin also presents itself as a possible adjuvant therapeutic alternative. Clinical trials suggest that oral melatonin supplementation can improve the clinical outcomes of periodontal therapy, especially in individuals with associated systemic diseases, such as type 2 diabetes mellitus. This suggests an integrative approach that considers both infection control and the patient's systemic inflammatory status. The reduced presence of melatonin in the saliva of patients with periodontitis may also be related to altered neuroendocrine mechanisms, possibly influenced by chronic inflammatory stress itself. This reinforces the need for longitudinal studies investigating the causality and underlying mechanisms of this association.

Despite advances in understanding the role of melatonin in periodontitis, significant gaps remain, particularly regarding the molecular mechanisms involved and the standardization of salivary collection and measurement methods. Therefore, future studies should seek to elucidate these aspects, in addition to exploring safe and effective therapeutic interventions based on melatonin modulation.

5 CONCLUSION

Studies have demonstrated a relationship between low salivary melatonin levels in individuals with periodontal disease, however, further randomized clinical trials are needed to further study this relationship.

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