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O uso de melatonina como terapia adjuvante da periodontite: Uma revisão sistemática com meta análise e relatos de casos clínicos.

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Dissertação apresentada ao Programa de Pós-Graduação em Ciências Aplicadas à Saúde, da Universidade Federal de Juiz de Fora, Campus Governador Valadares, como requisito parcial à obtenção do título de Mestre em Ciências Aplicadas à Saúde, área de concentração Biociências.

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RESUMO

A periodontite, uma doença que afeta os tecidos de sustentação dos dentes, está associada ao estresse oxidativo e a condições metabólicas como a obesidade. Este distúrbio metabólico afeta a resposta imune, promove desequilíbrios inflamatórios e agrava a destruição tecidual periodontal. Além disso, baixos níveis de melatonina têm sido correlacionados à obesidade e à periodontite, criando um ambiente pró-inflamatório sistêmico. A melatonina, possui propriedades antioxidantes, imunomoduladoras e anti-inflamatórias que podem potencialmente melhorar os resultados da terapia periodontal não cirúrgica (TPNC). Este estudo teve como objetivo avaliar a eficácia da melatonina como adjuvante à TPNC em indivíduos com obesidade e doença periodontal. Realizou-se uma revisão sistemática com meta-análise, registrada no PROSPERO (CRD42023472889), incluindo 15 estudos que investigaram parâmetros clínicos e bioquímicos. Foram avaliados 845 sítios periodontais (424 tratados com TPNC associada à melatonina e 421 tratados com TPNC isolada ou placebo). A busca incluiu cinco bases de dados principais e literatura cinzenta. O risco de viés foi analisado com a ferramenta RoB 2.0, e a qualidade das evidências foi avaliada pelo GRADE.Os resultados mostraram melhorias significativas nos parâmetros clínicos, como profundidade de sondagem (PS), nível de inserção clínica (NIC), índice gengival (IG) e índice de placa (IP), além de redução de biomarcadores pró-inflamatórios (IL-1β, IL-6, TNF-α), RANKL e HbA1c no grupo melatonina + TPNC. Embora a certeza das evidências tenha sido classificada como baixa a moderada, a maioria dos estudos apresentou baixo risco de viés. Os Relatos de casos clínicos complementaram os achados, utilizando um gel experimental de melatonina 1% em um modelo de boca dividida. Após três meses de acompanhamento, observou-se melhora nos parâmetros clínicos em comparação ao grupo controle tratado com gel placebo. A melatonina mostrou potencial como adjuvante à TPNC, promovendo benefícios clínicos e reduzindo a inflamação sistêmica. No entanto, mais estudos são necessários para estabelecer protocolos de administração, dosagens ideais e efeitos a longo prazo, especialmente em pacientes com obesidade e periodontite.

Palavras-chave: Antibacterianos, periodontite, obesidade, melatonina.

ABSTRACT

Periodontitis, a disease that affects the supporting tissues of the teeth, is associated with oxidative stress and metabolic conditions such as obesity. This metabolic disorder impacts the immune response, promotes inflammatory imbalances, and exacerbates periodontal tissue destruction. Additionally, low melatonin levels have been correlated with obesity and periodontitis, creating a systemic pro-inflammatory environment. Melatonin, a hormone secreted by the pineal gland and oral tissues, possesses antioxidant, immunomodulatory, and anti-inflammatory properties that may potentially improve the outcomes of non-surgical periodontal therapy (NSPT). This study aimed to evaluate the effectiveness of melatonin as an adjuvant to NSPT in individuals with obesity and periodontal disease. A systematic review with meta-analysis was conducted, registered in PROSPERO (CRD42023472889), including 15 studies investigating clinical and biochemical parameters. A total of 845 periodontal sites were assessed (424 treated with NSPT combined with melatonin and 421 treated with NSPT alone or placebo). The search covered five major databases and gray literature. The risk of bias was analyzed using the RoB 2.0 tool, and the quality of evidence was assessed using the GRADE framework. The results showed significant improvements in clinical parameters such as probing depth (PD), clinical attachment level (CAL), gingival index (GI), and plaque index (PI), as well as reductions in pro-inflammatory biomarkers (IL-1β, IL-6, TNF-α), RANKL, and HbA1c in the melatonin + NSPT group. Although the certainty of evidence was classified as low to moderate, most studies demonstrated a low risk of bias. Case reports complemented these findings, utilizing an experimental 1% melatonin gel in a split-mouth model. After three months of follow-up, improvements in clinical parameters were observed compared to the control group treated with a placebo gel. Melatonin has shown potential as an adjuvant to NSPT, promoting clinical benefits and reducing systemic inflammation. However, further studies are needed to establish administration protocols, optimal dosages, and long-term effects, particularly in patients with obesity and periodontitis.

Keywords: Antibacterials, periodontitis, obesity, melatonin.

SUMÁRIO

1 INTRODUÇÃO

A periodontite é a sexta doença mais prevalente globalmente, afetando cerca de 9,8% da população adulta global (GBD 2017 Oral Disorders Collaborators, 2020); resultado de manifestações inflamatórias crônicas devido ao acúmulo de biofilme; a presença de leucócitos polimorfonucleares (PMNs) e macrófagos nos tecidos periodontais apresentando elevado consumo de O2. O estresse oxidativo poderia ser uma das etiologias responsáveis pelo dano tecidual na periodontite (Wang, Y *et al.,* 2017).

Nos últimos 50 anos a obesidade tem aumentado sua prevalência em todo o mundo, atingindo níveis pandêmicos representando um grande desafio para a saúde porque aumenta consideravelmente o risco de doenças como diabetes mellitus tipo 2 (DM-2), doença hepática gordurosa, hipertensão, infarto do miocárdio, acidente vascular cerebral, demência, osteoartrite, apneia obstrutiva do sono e vários tipos de câncer (Blüher M. 2019),e na cavidade oral a periodontite (Zhao *et al.,* 2022), contribuindo assim para um declínio na qualidade de vida e na expectativa de vida.

Uma revisão sistemática com meta-análise publicada em 2022 reconhece a obesidade como um distúrbio metabólico significativo que está associado à perda de tecidos periodontais (Kim *et al.,* 2022), afetando as respostas imunes devido a um desequilíbrio nos níveis de citocinas pró-inflamatórias no plasma destes indivíduos (Abu-Shawish *et al*., 2022; Zorena *et al.,* 2020).

O tecido adiposo é um tipo de tecido conjuntivo composto por: adipócitos, pré-adipócitos, fibroblastos, células estromais e macrófagos (Lee *et al*., 2019; Flehmig *et al.,* 2014), que possuem diversas funções, dentre elas a regulação do funcionamento do sistema imunológico e endócrino. Existem diversos tipos de depósito de tecido adiposo; e o tecido adiposo branco visceral - vWAT (Lee *et al.,* 2019; Flehmig *et al.,* 2014; Cinti 2018) está relacionado à resistência à insulina, inflamação, dislipidemia, obesidade e DM-2 causada pela sua expansão patogênica (Zhao *et al.,* 2022; Zorena *et al.,* 2020; Lee *et al*., 2019), explicando assim a relação entre obesidade e doença periodontal.

A melatonina é uma indolamina secretada principalmente pela glândula pineal (Zorena *et al.,* 2020) como também pelos tecidos gengivais e glândulas salivares (Balaji *et al*., 2021), envolvido em inúmeras ações, como antioxidante,

anti-inflamatório (Szewczyk-Golec *et al.,* 2015, Lu *et al.,* 2021). e diminui a produção de adipocinas pelo WAT (Szewczyk-Golec *et al.,* 2015). A melatonina possui diferenciais pró e anti-inflamatórios capazes de promover, regular e neutralizar a inflamação simultaneamente. (Ragdona *et al.,* 2010).

Atualmente a instrumentação subgengival não cirúrgica (ISNC) é considerada o pradrão ouro para o tratamento da periodontite (Lu *et al.,* 2021; Sanz *et al*., 2021; Liu *et al.,* 2022); porém terapias adjuvantes têm sido consideradas para melhorar e estabilizar os resultados clínicos conseguidos pela ISNC, das quais podemos destacar o emprego de melatonina.

Na literatura é possível encontrar estudos relatando que os níveis de melatonina em indivíduos com periodontite grave foram mais baixos em comparação aos indivíduos saudáveis, levando a investigações sobre possíveis efeitos da suplementação exógena de melatonina após ISNC na periodontite (Balaji *et al*., 2021; Wang *et al.,* 2022). Há ainda alguns trabalhos onde a obesidade também está relacionada a uma deficiência dos níveis de melatonina (Szewczyk-Golec *et al.,* 2015; Cipolla-Neto *et al.,* 2014). Uma recente revisão sugere um possível papel da melatonina em doenças metabólicas como obesidade (Ramirez *et al.,* 2021).

O objetivo deste estudo foi realizar uma revisão sistemática com meta análise e o relato de uma série de casos que justifique uma possível utilização da melatonina como tratamento adjuvante a TPNC em indivíduos com obesidade e doença periodontal.

2 DESENVOLVIMENTO

2.1 ARTIGO CIENTÍFICO 1

O artigo científico foi enviado para publicação no periódico Journal of Periodontal Research. A estruturação do artigo baseou-se nas instruções aos autores preconizadas pelo periódico (ANEXO 1).

Is melatonin an effective adjunct to non-surgical periodontal therapy in patients with periodontitis? A systematic review and meta-analysis.

Abstract

Aim: This systematic review and meta-analysis aimed to assess the efficacy of melatonin as an adjunct to non-surgical periodontal therapy (NSPT) in improving clinical outcomes—probing depth (PD), clinical attachment level (CAL), gingival index (GI), plaque index (PI), and bleeding on probing (%). It also evaluated biochemical markers, including inflammatory biomarkers (IL-1β, IL-6, TNF-α, RANKL) and HbA1c levels.

Methods: This review was registered in PROSPERO (CRD42023472889). A systematic search was conducted across five databases (MEDLINE/PubMed, Web of Science, Scopus, Embase, and LILACS) for articles published up to September 2024. Grey literature sources, including ProQuest and ClinicalTrials.gov, were also reviewed. Reference lists of included studies were manually searched for additional articles. The risk of bias was assessed using the RoB 2.0 tool, and the certainty of evidence was evaluated using the GRADE framework. Meta-analysis was performed with RevMan 5.4.

Results: Fifteen studies met the eligibility criteria, encompassing 845 periodontal sites: 424 treated with melatonin combined with NSPT and 421 treated with NSPT alone or placebo. Meta-analysis demonstrated significant improvements in periodontal parameters (PD, CAL, GI, PI) favoring melatonin + NSPT compared to the control group across different follow-up periods. Additionally, melatonin supplementation significantly improved biochemical outcomes, including reductions in pro-inflammatory biomarkers (IL-1β, IL-6, TNF-α), RANKL, and

HbA1c levels. Most included studies showed a low risk of bias, though the certainty of evidence was graded as low to moderate.

Conclusion: This systematic review and meta-analysis indicated that melatonin as an adjunct to NSPT improves clinical outcomes and reduces systemic inflammation, as evidenced by lower levels of pro-inflammatory biomarkers and HbA1c. While the certainty of the evidence is limited, melatonin shows the potential to enhance periodontal therapy outcomes. However, further studies are necessary to improve the evidence and determine optimal administration protocols, dosage, and long-term effects.

Keywords: Periodontal diseases; periodontal index; sickle cell anemias; sickle cell disease.

1. INTRODUCTION

Periodontitis is recognized as the sixth most prevalent chronic condition worldwide, affecting approximately 9.8% of the adult population.[1] This multifactorial disease is characterized by chronic inflammation, initiated by the accumulation of microbial biofilm. This process activates host immune responses, predominantly involving polymorphonuclear leukocytes (PMNs) and macrophages. These immune cells contribute to increased oxygen consumption and the subsequent production of reactive oxygen species (ROS). Notably, oxidative stress has been identified as a key factor in the progression and destruction of periodontal tissues.[2]

Non-surgical periodontal therapy (NSPT) is considered the gold standard in periodontal therapy for biofilm control and achieving clinical improvements.[3-5] However, the quest for adjunctive therapeutic therapies to enhance and prolong the clinical benefits of NSPT has intensified.[6] Among the various adjuvant options, melatonin has emerged as a promising agent.[7]

Melatonin is an endogenous indoleamine primarily synthesized by the pineal gland,[8] and exhibits multifunctional properties, including the regulation of circadian rhythms, modulation of energy metabolism, and antioxidant and anti-inflammatory effects.[3,9] Additionally, melatonin has demonstrated protective effects against oxidative stress-induced cellular damage, angiogenesis,[10] and immunomodulation,[11] inhibiting bone resorption and stimulating osteoblastic

differentiation.[10] Additionally, in vitro studies have shown its ability to inhibit the growth of *Porphyromonas Gingivalis*, an important periodontal pathogen.[12]

A previous systematic review concluded that melatonin supplementation significantly enhances periodontal clinical parameters, supporting its potential as an adjunctive therapy in NSPT.[5] Nevertheless, the review included only seven studies, and most of the analyses were based on just five to two studies, respectively. Additionally, the authors acknowledged that the limited number and quality of included studies might affect the robustness of their conclusions, emphasizing the need for further randomized controlled trials (RCTs). Since then, news RCTs have been published on this topic,[13-19] underscoring the necessity of re-evaluating these findings to verify whether the reported improvements remain consistent. Therefore, this present systematic review and meta-analysis aim to provide an updated and comprehensive synthesis of the available evidence, focusing on the efficacy of melatonin as an adjunct to NSPT in improving and stabilizing clinical periodontal outcomes. The hypothesis tested was that melatonin use does not improve clinical and biochemical markers outcomes following NSPT.

2. MATERIALS AND METHODS

2.1 Protocol and Registration

This systematic review was conducted following the Cochrane Handbook for Systematic Reviews of Interventions[20] and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A detailed methodological protocol was developed in accordance with PRISMA-P[21] and registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42023472889.

2.2 Eligibility Criteria

The eligibility criteria were defined based on the research question, which was developed using the Participants, Intervention, Comparison, Outcomes, and Study Design (PICOS) framework. The formulated question was: *“Do patients with periodontal disease undergoing adjunctive melatonin therapy in* NSPT *achieve enhanced clinical outcomes and biochemical levels compared to those receiving* NSPT *alone?”*.

P: Adults (≥ 18 years) with periodontal diseases who underwent NSPT, regardless of gender.

I: NSPT with adjunctive melatonin therapy (oral or topical).

C: NSPT alone or with a placebo.

O: Probing depth (PD), clinical attachment level (CAL), gingival index (GI), plaque index (PI), bleeding on probing (BOP [%]), and biochemical markers.

S: RCTs only.

Studies were excluded if they did not perform the NSPT in either test or control groups, observational studies, case reports, reviews, letters to the editor, or animal studies. No restrictions were applied regarding the publication period or language of publication.

2.3 Literature Search Strategy and Study Selection

Searches were conducted across several electronic databases, including MEDLINE via PubMed, Embase, Web of Science, Scopus, and LILACS. The search strategy combined Medical Subject Headings (MeSH) and free-text terms. Detailed search strategies for each database are provided in Supplemental File 1. In addition, gray literature was examined using ProQuest and ClinicalTrials.gov, and a manual search of the reference list of relevant studies was performed.

All search results were exported to Rayyan QCRI, a reference management program.[22] The initial comprehensive search was independently conducted by two reviewers (O.N.R.P. and Z.G.) according to the eligibility criteria, based on title and abstracts. Discrepancies in study selection were resolved by consensus with a third reviewer (C.A.A.L.), ensuring methodological rigor and consistency. The initial search was carried out in September 2023, with an updated search completed in September 2024 to include the most recent publications.

2.4 Data Extraction

Data extraction was conducted by a single author (O.N.R.P.) from all eligible studies, with a second author (C.A.A.L.) reviewing the extracted data to ensure accuracy. The extracted variables included the following: author and year of publication, mean age, sample size (test and control groups), presence of

systemic diseases, diagnosis, administration details (dosage and period), follow-up examination, and evaluated clinical outcomes.

2.5 Risk of Bias

The risk of bias was evaluated using the RoB 2.0 tool, a standardized instrument specifically designed for randomized controlled trials (RCTs). This tool systematically examines five key domains where bias may impact study outcomes: (1) the randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) outcome measurement, and (5) selection of the reported result. Each domain was analyzed through signaling questions that identified relevant methodological characteristics. Based on these responses, an algorithm provided an overall judgment for each domain, classifying the risk of bias as “Low Risk,” “Some Concerns,” or “High Risk”.[23]

2.6 Data Synthesis

Meta-analyses for PD, CAL, GI, PI, and biochemical makers were conducted using the inverse variance method. As these outcomes represent continuous variables, the analyses used mean differences (MD) or standardized mean differences (SMD). For BOP (%) the dichotomous analysis was performed using Risk Ratio (RR). Both analyses were performed considering 95% confidence intervals (CIs), considering a p-value below 0.05 indicating statistical significance. A random-effects model was applied in cases of substantial heterogeneity. The analysis was performed using Review Manager software (RevMan 5.4; The Nordic Cochrane Center, The Cochrane Collaboration, 2014). Data from graphical representations in studies were extracted using WebPlot Digitizer (Automeris LLC, Frisco, Texas).

2.7 Certainty of evidence

The certainty of the evidence was assessed following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. This framework evaluates the level of evidence certainty for each outcome individually, considering factors such as study design, heterogeneity, indirectness, imprecision, and potential publication bias. Each outcome was categorized into one of four levels of certainty: high, moderate, low, or very low.

The GRADEpro GDT software (https://gdt.gradepro.org/app/) was employed to generate the Summary of Findings tables.[24]

2.8 Additional analysis

Additionally, an analysis was conducted to assess intra-examiner agreement during the study selection phase.[25]

3 RESULTS

3.1 Study Selection

A total of 827 articles were identified through electronic database searches: 139 from MEDLINE via PubMed, 178 from Web of Science, 235 from Scopus, 216 from Embase, 19 from LILACS, and 40 from ProQuest. After removing duplicates, 423 articles remained for title and abstract screening. Based on the eligibility criteria, 20 articles were selected for full-text review. Of these, five studies were excluded as they did not address the association of melatonin with NSPT treatment in patients with periodontitis.[26-30] Ultimately, 15 studies were included for both quantitative and qualitative synthesis,[13-16,18,19,31-38] with three studies originating from the same research group using the same patient cohort but with different outcomes.[18,19,36]

The article selection process demonstrated substantial agreement between reviewers, achieving a kappa value of 0.86, which reflects a high level of consistency.[39] The flowchart summarizing the search strategy and selection process is presented in Figure 1.

3.2 Characteristics of Included Studies

Thirteen RCTs were included in the analysis, two of which employed a split-mouth design.[16,31] Most studies reported double-blind,[15,16,18,19,33,35,36,38] while one study reported a triple-blind design.[34] The studies assessed 845 periodontal sites, with 424 sites treated with melatonin associated with NSPT and 421 sites treated with NSPT alone or placebo. The mean age varied across the included studies, ranging from 23 to 55 years.

Some studies reported that patients presented with periodontitis stage I,[13] II,[15,31] III,[14-16,34] or IV[13] periodontitis, None of the studies assessed periodontal conditions in the context of furcation defects. Others included patients with mild

to moderate,[18,19,36] or moderate to severe periodontitis.[32,35,37] Five studies specifically evaluated patients with type 2 diabetes.[15,18,19,33,36]

Eleven studies considered the evaluation of oral melatonin varying the dosage between 1, 2, 3, 6, and 10 mg during 4 to 8 weeks.[14,15,18,19,32-38] Four studies considered the evaluation of topic gel melatonin with a concentration of 1, 2, and 5% applied intra-pocket after NSPT.[13,16,17,31] The follow-up period of the included studies varied from 1 to 6 months, and the clinical outcomes evaluated were PD, CAL, GI, PI, BOP, PDI, CPI, and biochemical levels, including inflammatory biomarkers (IL-1β, IL-6, TNF-α, RANKL) and HbA1c levels. All included studies reported in their conclusion a positive effect on the clinical and biochemical levels of the use of melatonin after NSPT (Table 1).

3.3 Meta-analysis

The meta-analysis demonstrated no significant differences between the baseline outcomes for the NSPT + Melatonin group and the NSPT group alone (P>0.05), confirming appropriate pairing between the evaluated groups.

The meta-analysis revealed significant improvements in PD favoring the intervention group (NSPT + Melatonin) compared to the control group (NSPT alone). These improvements were observed at 2 months (P<0.00001; MD = -1.80; CI: -2.12 to -1.47), 3 months (P=0.002; MD = -0.78; CI: -1.27 to -0.28), and 6 months (P=0.010; MD = -0.64; CI: -1.12 to -0.15) (Figure 2).

Similar to PD, the meta-analysis indicated favorable outcomes for CAL in the intervention group. Significant differences were found in 2 months (P<0.00001; MD = -1.48; CI: -1.74 to -1.21), 3 months (P=0.008; MD = -0.48; CI: -0.83 to -0.12), and 6 months (P=0.003; MD = -0.64; CI: -1.30 to -0.28) (Figure 3).

For GI, significant differences favoring NSPT + Melatonin was observed at 1 month (P=0.002; MD = -0.29; CI: -0.47 to -0.10) and 3 months (P=0.01; MD = -0.30; CI: -0.53 to -0.07). However, no significant differences were found between groups at 6 months (P=0.33; MD = -0.10; CI: -0.29 to 0.10) (Figure 4).

Significant improvements in PI were noted for the intervention group at 3 months (P=0.03; MD = -0.61; CI: -1.17 to -0.06) and 6 months (P=0.006; MD = -0.18; CI: -0.31 to -0.05) (Figure 5).

Dichotomous analysis of BOP (%) revealed a significant difference favoring the intervention group only at 2 months (P=0.003; RR = 0.68; CI: 0.53 to 0.88). No significant differences were observed at 3 months (P=0.33; RR = 0.73; CI: 0.38 to 1.38) or 6 months (P=0.45; RR = 0.76; CI: 0.38 to 1.53) (Figure 6).

The biochemical markers analysis indicated significant improvements for the NSPT + Melatonin group compared to the control group, for IL-1β: P<0.00001; SMD = -1.98; CI: -2.36 to -1.61; IL-6: P<0.00001; SMD = -0.98; CI: -1.32 to -0.65; TNF-α: P=0.03; SMD = -1.52; CI: -2.92 to -0.12; and RANKL: P=0.0006; SMD = -0.73; CI: -1.15 to -0.32. Additionally, a significant reduction in HbA1c levels was observed in the intervention group compared to the control group (P=0.02; SMD = -2.38; CI: -4.40 to -0.35) (Supplemental File 2).

3.4 Risk of Bias

Most of the studies included showed an overall risk of bias according to RoB 2.0.[14-16,18,19,31-35] Some studies were assessed as having some concerns because they did not present information about the randomization process or due to deviations from the intended intervention.[17,37,38] Additionally, one study was assessed with a high risk of bias due to presenting three domains with some concerns[13] (Figure 7).

3.5 Certainty of Evidence

The certainty of evidence, assessed using the GRADE approach, ranged from low to moderate across the evaluated outcomes, with one outcome classified as very low. Most outcomes were downgraded due to inconsistency and imprecision, while indirectness was downgraded by one level only for HbA1c outcomes before and after treatment. No publication bias was detected in the included studies. Further details on the GRADE certainty evidence can be found in Supplemental File 3.

4. DISCUSSION

The hypothesis tested was rejected, as significant improvements were observed in all periodontal clinical parameters and biochemical markers levels after the use of melatonin combined with NSPT. The results of the meta-analysis corroborated with the findings of individual studies included in this systematic

review. Melatonin, an indolamine primarily produced and secreted by the pineal gland,[7] is also synthesized in extrapineal sites, including the oral cavity, where it is secreted by salivary glands and gingival tissues.[11,40]

A previous systematic review reported reduced melatonin levels in patients with chronic periodontitis, suggesting that melatonin is consumed and degraded during its antioxidant and immunomodulatory activities in chronic periodontitis.[2,40] The relationship between periodontitis severity and substances with antioxidants and anti-inflammatory potential remains controversial, underscoring the need for further investigations. Recent studies report that the beneficial effects of melatonin for patients with periodontitis could be attributed to the potential anti-inflammatory, antioxidant, immunomodulatory, and osteomodulatory properties of melatonin.[5,15,16,31,40]

Two included studies[18,31] demonstrated melatonin's antioxidant effects by showing a significant increase in total antioxidant capacity markers compared to the control group. Furthermore, beyond the antioxidant properties recent research highlights the anti-inflammatory, and immunomodulatory properties of melatonin.[18,41] In periodontitis, the overexpression of reactive oxygen and nitrogen species induces stress in periodontal tissues, leading to structural damage.[2,16,35] The host's ability to scavenge these reactive species is a crucial defensive mechanism against periodontal tissue damage. Notably, melatonin presents dual roles as both a pro- and anti-inflammatory agent allowing it to regulate and counteract inflammation simultaneously.[42]

Targeting reactive species, modulates the release of pro-inflammatory cytokines in periodontal tissues. This is supported by the meta-analysis, which revealed reduced levels of IL-1β, IL-6, and TNF-α following melatonin use in combination with NSPT. This effect may be due to melatonin suppression of NF-kappa B transcription, which downregulates the production of key pro-inflammatory cytokines, such as IL-1β and TNF-α.[11,43] Additionally, melatonin also promotes osteoblastic differentiation and inhibits osteoclastic activity by downregulating RANKL.[16] Periodontal bone loss results from an imbalance between RANKL and OPG, the natural antagonist of RANKL.[14] The binding of RANKL to its receptor RANK on the membrane cell of preosteoclasts and osteoclasts triggers osteoclast activation, increasing bone resorption and reducing bone formation.[14,44] Melatonin's ability to inhibit osteoclastogenesis may

contribute to preventing periodontal disease progression and preserving tooth integrity.[17]

Clinically, the combination of melatonin with NSPT improved all evaluated periodontal parameters, particularly the reestablishment of periodontal tissue. However, most studies also reported improvements in periodontal parameters following NSPT alone or with a placebo compared to baseline, highlighting the efficacy of standard treatment in the progression of tissue damage.[15,16,31,32] Nonetheless, NSPT alone may fail to halt progressive attachment loss in certain cases, emphasizing the importance of adjunctive therapeutic agents, such as melatonin, to enhance clinical outcomes of periodontitis.[16,35]

Five studies assessed patients with diabetes,[15,18,19,33,36] which is significant given diabetes exacerbates susceptibility to and the severity of periodontal diseases.[45] Poor glycemic control correlates with more severe periodontal disease progression.[46] A study of 2,973 systemically healthy individuals found that severe periodontal tissue destruction was associated with HbA1c levels nearly five times higher than in individuals with healthy periodontal tissue.[47] Studies combining melatonin with NSPT in type 2 diabetic patients and periodontitis showed reduced HbA1c levels after treatment, suggesting melatonin may aid in controlling hyperglycemia in chronic periodontitis.[18] This finding was confirmed by quantitative analysis in this systematic review, supporting melatonin's role in managing HbA1c in the context of periodontitis.

This systematic review has some limitations, which warrant cautious interpretation of results. A primary limitation is the lack of standardization in melatonin administration methods, either systemic or topical. Most studies investigated systemic melatonin via oral administration, while only four studies evaluated topical gel applications. Although all included studies reported potential benefits of melatonin regardless of administration route, this variability could influence the overall analysis. A sub-analysis isolating administration method was not feasible due to the limited number of studies with consistent follow-up periods and outcomes. Future studies should address the influence of administration routes on clinical periodontal parameters.

Another limitation pertains to variations in melatonin dosage and treatment duration. Regarding the period, the studies varied from 4 and 8 weeks of oral or topical administration. However, concerning the dosage, this difference was more

pronounced. The oral concentration ranged from 1 mg to 10 mg, while the topical gel ranged from 1% to 5%. The possible explanation for the study that considered a higher dosage of oral melatonin (10 mg) compared to other studies should be attributed to the fact that this melatonin dose was administrated for insomniac patients included in their study.[35] Thus, this high dose would possibly be more related to the sleep disorder condition and not specifically to periodontal adjunct therapy.

Only six studies reported data on adverse effects, with five showing no adverse effects of melatonin during the study period.[14,16,31,33,34] One study,[35] which used a higher oral dosage, reported some events, including headache, dizziness, nausea, constipation, diarrhea, and abdominal cramps, for both melatonin and placebo groups. This highlights the importance of the melatonin dosage, as excessive doses may lead to other adverse effects reported in the literature such as excessive sedation, cognitive disorders, and nocturnal hypotension.[48] A recent systematic review, including fifty with dosages ranging from 0.3 mg to 1,600 mg daily, found that nearly 50% reported at least one adverse event, typically minor and short-lived, such as fatigue, mood changes, or psychomotor and neurocognitive performance. Few studies noted endocrine or cardiovascular effects, which were influenced by dosage, timing, and drug interactions.[49] This last is particularly relevant for patients with chronic conditions including periodontal disease, where drug interactions are a concern. Despite this, melatonin supplementation appears generally safe.[49] However, to minimize adverse effects or interactions, reducing melatonin dosage in periodontitis cases should be considered to optimize treatment effectiveness. The optimal dose and timing of melatonin administration (oral or topical) as an adjunct therapy for periodontitis still require further investigation to identify the most effective lower dose. Currently, no studies have evaluated the impact of different dosages or treatment periods on clinical periodontal outcomes. Therefore, identifying a safe, effective dose to improve clinical outcomes is crucial. Ultimately, the certainty of evidence ranged from low to moderate for the evaluated outcomes, limiting data interpretation. While all evidence supports the benefit of melatonin with NSPT, further well-designed randomized studies with larger samples are needed to confirm these findings and strengthen the evidence base.

5. CONCLUSION

This systematic review and meta-analysis revealed that melatonin use in NSPT provides significant clinical and biochemical benefits. Notable improvements were observed in clinical parameters such as PD, CAL, GI, and PI were observed. Melatonin also significantly reduced pro-inflammatory biomarkers (IL-1β, IL-6, TNF-α) RANKL, and HbA1c levels, indicating potential systemic benefits. However, the certainty of evidence ranged from low to moderate. Therefore, further high-quality studies focusing on administration methods, dosages, and treatment periods are recommended to confirm these findings and assess the long-term effects of melatonin in periodontal therapy.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in this study; data sharing is not applicable.

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FIGURES

Figure 1. Flowchart of search strategy

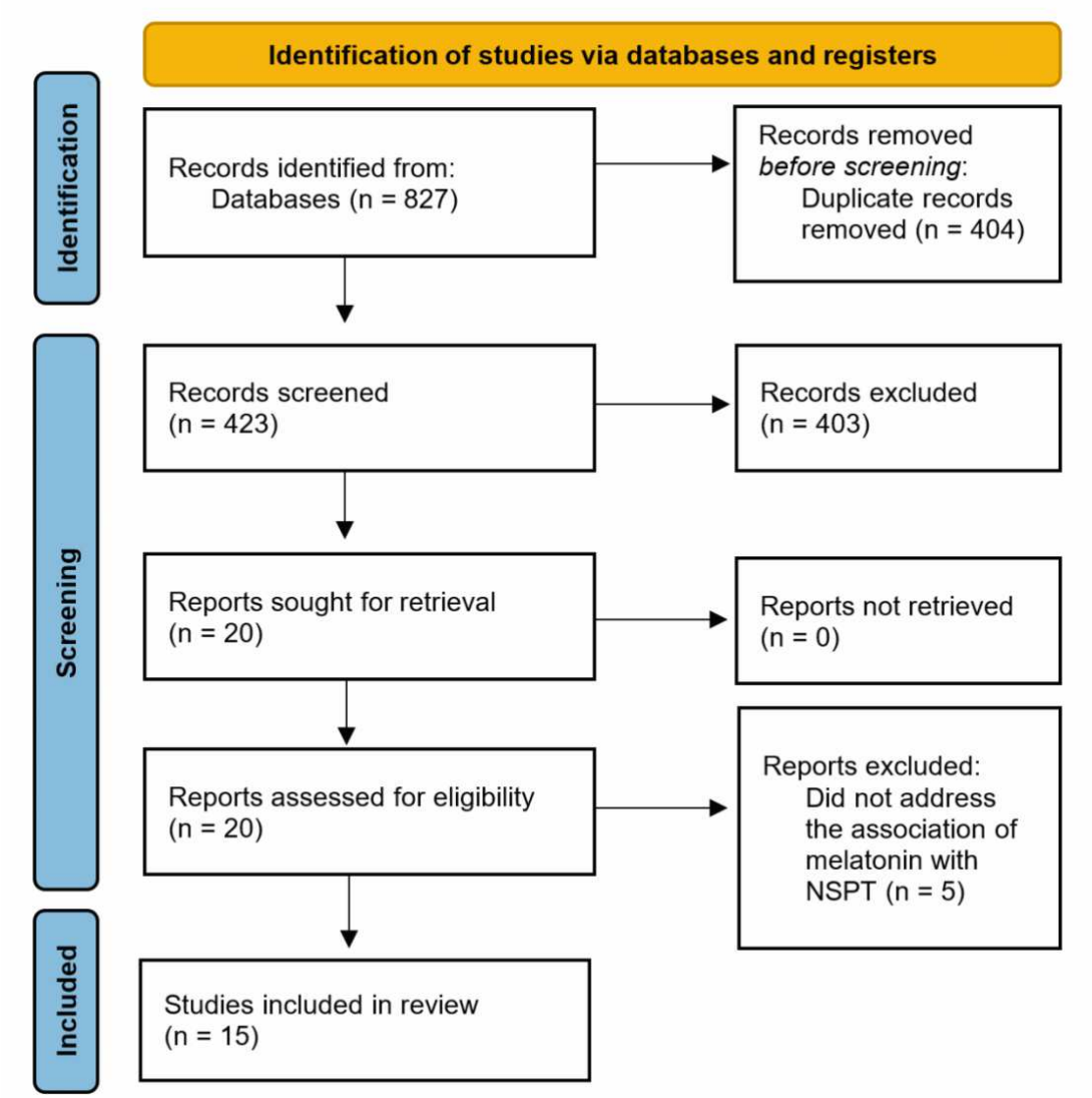


Figure 2. Forest plot comparing NSPT + Melatonin and NSPT for PD outcomes at baseline, 2 months, 3 months, and 6 months.

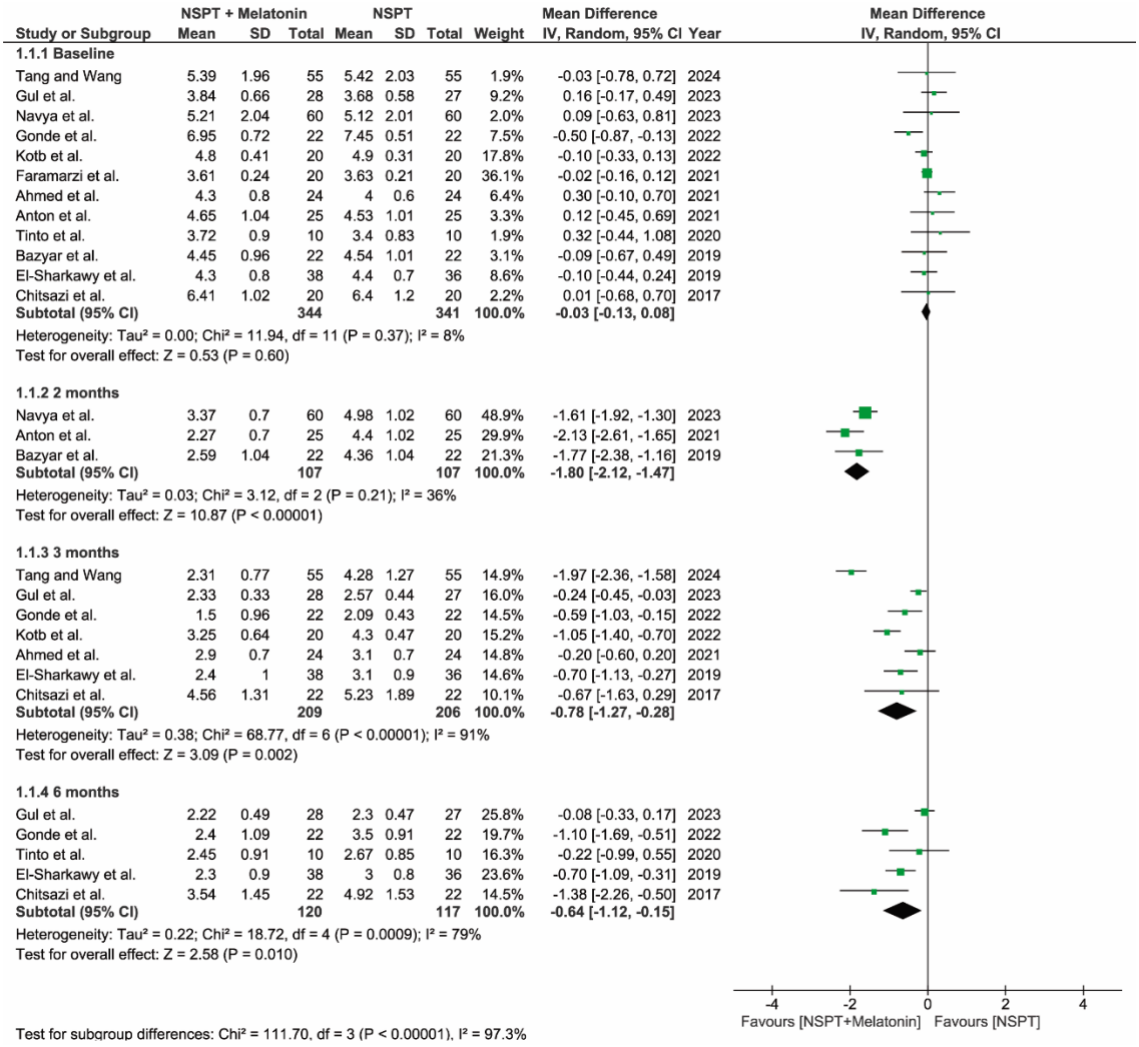


Figure 3. Forest plot comparing NSPT + Melatonin and NSPT for CAL outcomes at baseline, 2 months, 3 months, and 6 months.

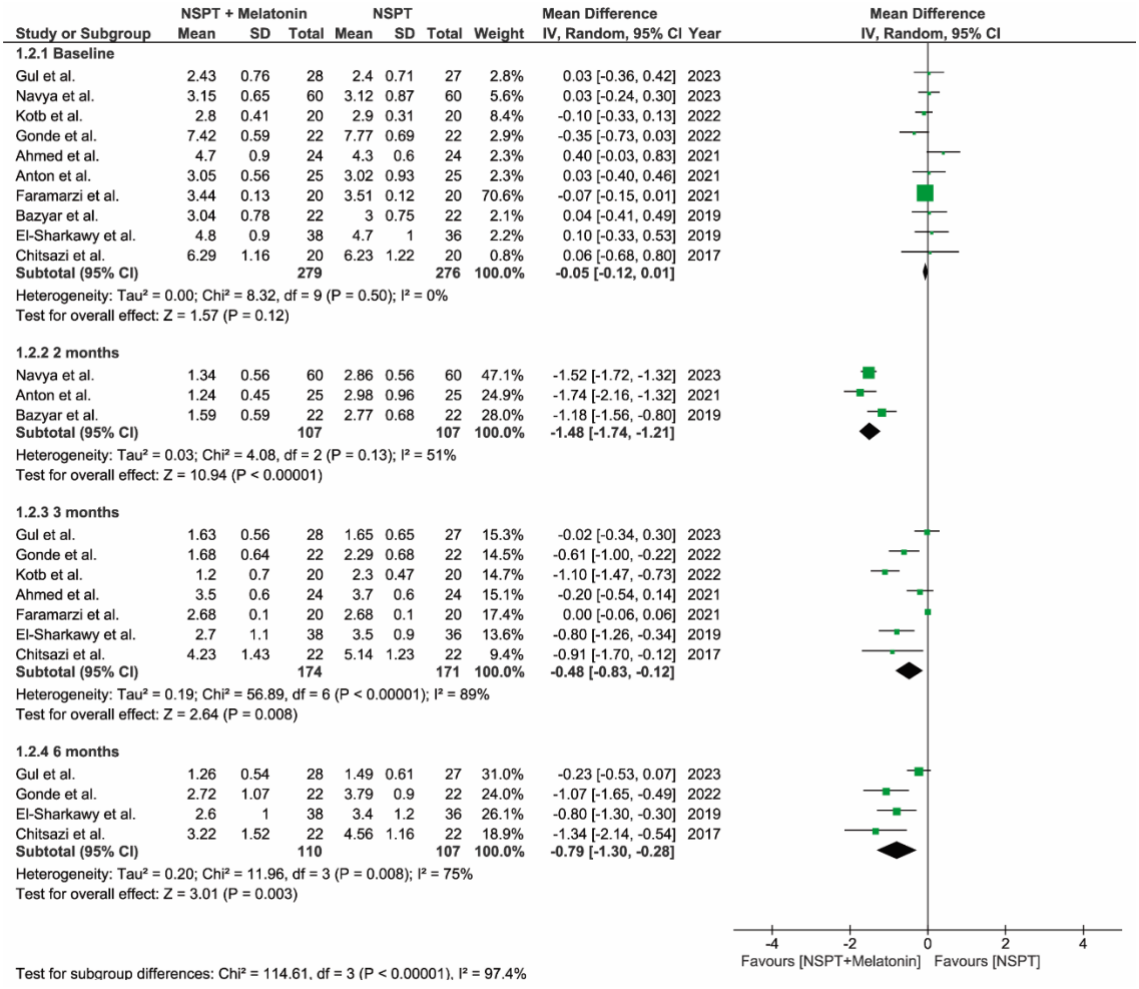


Figure 4. Forest plot comparing NSPT + Melatonin and NSPT for GI outcomes at baseline, 1 month, 3 months, and 6 months.

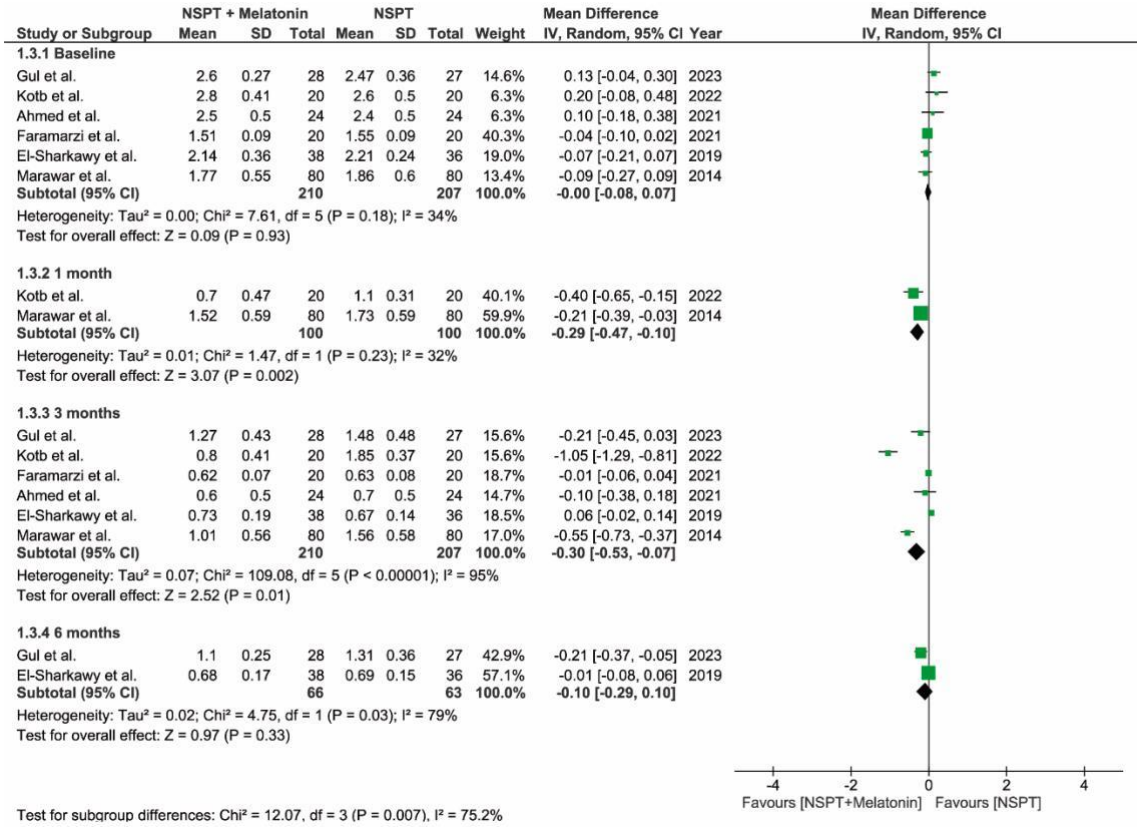


Figure 5. Forest plot comparing NSPT + Melatonin and NSPT for PI outcomes at baseline, 3 months, and 6 months.

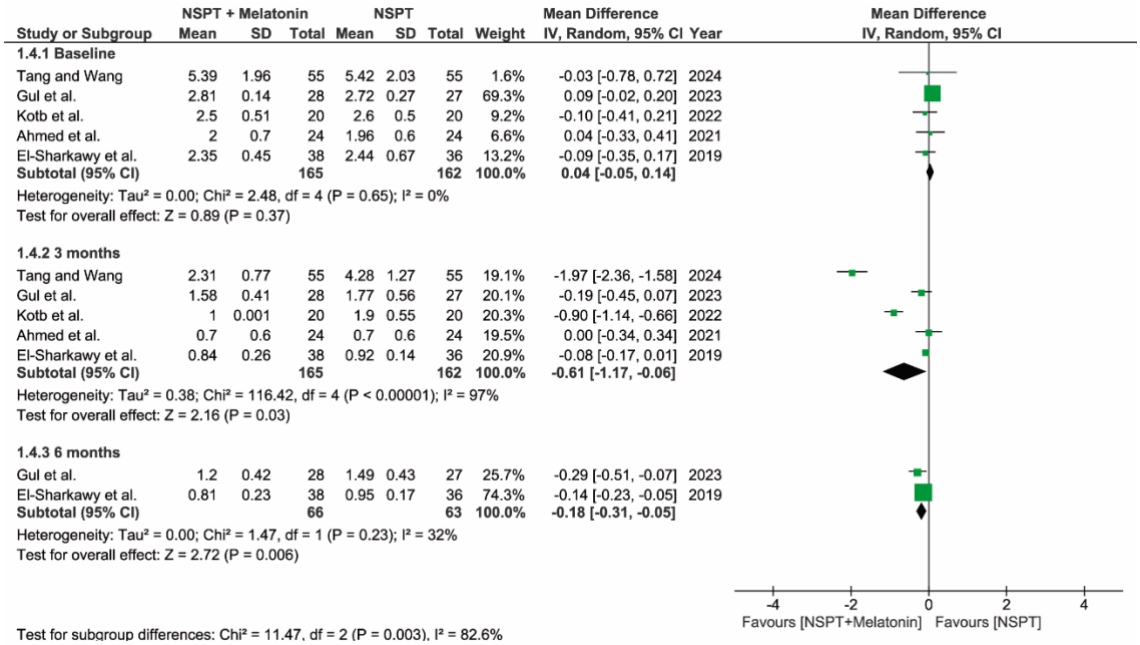


Figure 6. Forest plot comparing NSPT + Melatonin and NSPT for BOP (%) outcomes at baseline, 2 months, 3 months, and 6 months.

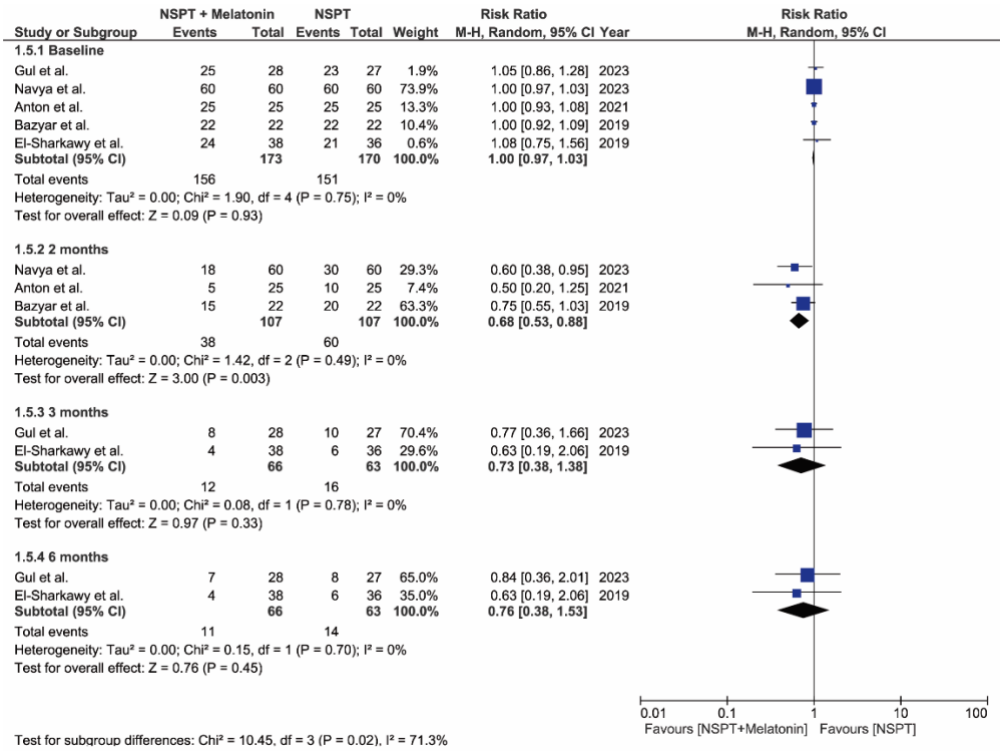


Figure 7. Risk of bias assessment using RoB 2.0 tool.

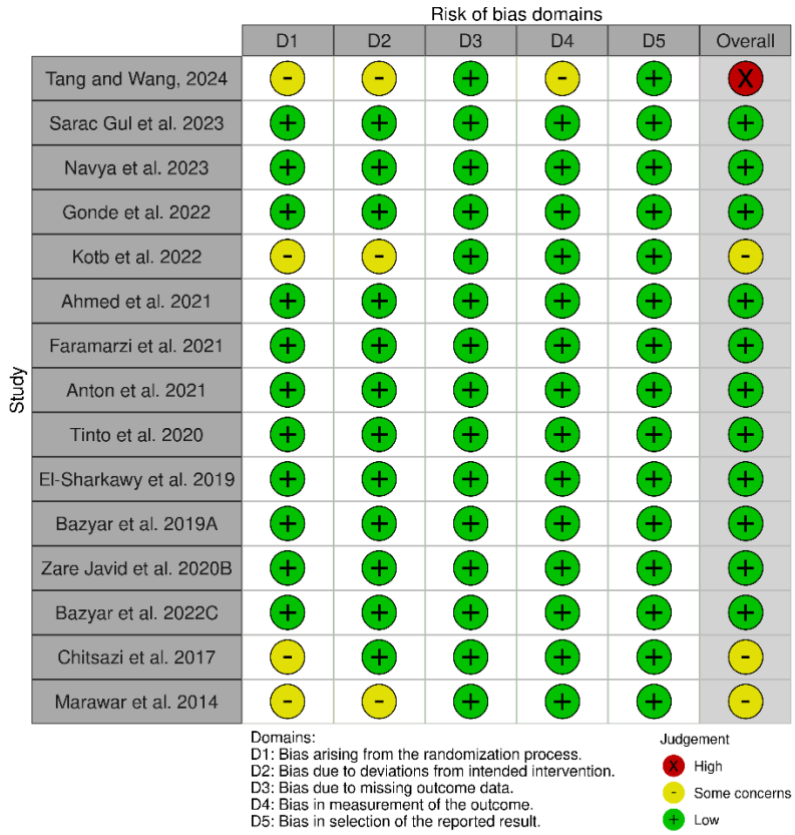


Table 1. Characteristics of included studies (n = 13)

Author/Year	Study design	Sample size	Mean age (Years)	Diagnosis	Administration/Dosage/Period	Follow-up	Clinical outcomes evaluated	Effect of melatonin
Tang and Wang 2024[13]	RCT	MEL: 55 CG: 55	MEL:32.08±4.76 CG: 31.94±5.11	Stage I or IV periodontitis	NSSI + MEL (1% gel; 0.5 to 2 ml per application) applied to the oral area once or twice a day	NR	PD, BOP, IL-1β, IL-6, TNF-α	Positive
Sarac Gul et al. 2023[14]	RCT	MEL: 28 CG: 27	MEL: 51.9±8.58 CG: 54.1±6.22	Stage III and IV periodontitis (grade C)	NSSI + MEL (oral, 6 mg) taken before bedtime for 4 weeks	3 months 6 months	PD, CAL, GI, PI, BOP, IL-1β, MMP-8, RANKL, OPG	Positive
Navya et al. 2023[15]	RCT double-blind	MEL: 60 CG: 60	MEL: 52,12±3,7 CG:: 51,12±3,4	Stage II and III periodontitis (type 2 diabetes)	NSSI + MEL (oral, 2 mg) taken before bedtime for 8 weeks	2 months	PD, CAL, GI e HbA1c	Positive
Gonde et al. 2022[16]	RCT double-blind split-mouth	MEL: 22 CG: 22	> 18 years.	Stage III periodontitis	NSSI + MEL (1% gel) applied intra-pocket after NSSI	3 months 6 months	PD, CAL, PI	Positive
Kotb et al. 2022[17]	RCT	MEL: 20 CG: 20	Range: 23 to 39	Periodontal diseases	NSSI + MEL (2% gel) applied intra-pocket after NSSI once weekly for 4 weeks	1 week 1 month 3 months	PD, PI, CAL, GI, RANKL, GCF	Positive
Ahmed et al. 2021[31]	RCT split-mouth	MEL: 24 CG: 24	Range: 32 to 55	Stage II periodontitis	MEL (5% gel) applied intra-pocket after NSSI, once a week for 4 weeks	3 months	PD, CAL, PI, GI TAC, MMP-9	Positive
Faramarzi et al. 2021[32]	RCT	MEL: 20 CG: 20	Range: 25 and 45	Moderate to severe periodontitis	NSSI + MEL (oral, 3 mg) taken once daily for 4 weeks	3 months	PD, CAL, GI	Positive
Anton et al. 2021[33]	RCT double-blind	MEL: 25 CG: 25	MEL: 53.24±3.4 CG: 52.21±3.1	Periodontal diseases (type 2 diabetes)	NSSI + MEL (oral, 3 mg) taken 1 hour before bedtime for 8 weeks	2 months	PD, CAL, BOP, H42bA1c	Positive
Tinto et al. 2020[34]	RCT triple-blind	MEL: 10 CG: 10	45.6	Stage III periodontitis	NSSI+ MEL (oral, 1 mg) taken before bedtime for 4 weeks	6 months	PD, BOP, PI	Positive
El-Sharkawy et al. 2019[35]	RCT double-blind	MEL: 38 CG: 36	MEL: 45.6 ± 7.1 CG: 46.7 ± 8.3	Moderate to severe periodontitis	NSSI + MEL (oral, 10 mg) taken 1 hour before bedtime for 8 weeks	3 months 6 months	PS, CAL, GI, TNF-α	Positive
Bazyar et al.[A] 2019[36] Zare Javid et al.[B] 2020[18] Bazyar et al.[C] 2022[19]	RCT double-blind	MEL: 22 CG: 22	MEL: 53,7±6,68 CG: 51,5±5,03	Mild and moderate periodontitis (type 2 diabetes)	NSSI + MEL (oral, 3 mg) taken 1 hour before bedtime for 8 weeks	2 months	[A]PD, CAL, BOP, GI, TNF-α , IL-6 [B]IL-1β, TAC, MDA, SOD, CAT, GPx [C]FBG, HbA1c, BMI, WC, HC, SBP, DBP	Positive
Chitsazi et al. 2017[37]	RCT	MEL: 20 CG: 20	41 (range: 23 to 65)	Moderate to severe periodontitis	NSSI + MEL (oral, 2 mg) daily for 4 weeks	3 months 6 months	PD, CAL, GI	Positive
Marawar et al. 2014[38]	RCT double-blind	MEL: 80 CG: 80	> 18 years	Periodontal diseases	NSSI + MEL (oral, 3 mg) daily at night for 4 weeks	1 month 2 months 3 months	GI, PDI, CPI	Positive

PD: Probing depth; CAL: Clinical attachment level; GI: Gingival index; PDI: Periodontal disease index; CPI: Community Periodontal Index; HbA1c: Glycosylated hemoglobin levels; TAC: Total antioxidant capacity; MDA: malondialdehyde; SOD: Super-oxide dismutase; CAT: Catalase; GPx: Glutathione perioxidase; BMI: Body mass index; WC: weight

and waist circumference; HC: hip circumference; FBG: fasting blood glucose; SBP and DBP: systolic and diastolic blood pressure; TAC: Total Antioxidant Capacity; MMP-9: Matrix Metalloproteinase-9.

Supplemental File 1. Advanced search strategy for each electronic database.

MEDLINE via PubMed

#1	((((((((((("Periodontal Diseases"[Mesh]) OR ("Periodontal Diseases")) OR ("Periodontal Disease")) OR ("Periodontitis"[Mesh])) OR ("Periodontitis")) OR ("Periodontal Attachment Loss"[Mesh])) OR ("Periodontal Attachment Loss")) OR ("Furcation Defects"[Mesh])) OR ("Furcation Defects")) OR ("Alveolar Bone Loss"[Mesh])) OR ("Alveolar Bone Loss")) OR ("Bone Defects")) OR ("Intrabony Defects")) OR ("Infrabony Defects")
#2	("Melatonin"[Mesh]) OR ("Melatonin")
#3	#1 AND #2

Web of science

#1	((((((((((((ALL=("Periodontal Diseases"[Mesh)) OR ALL=("Periodontal Diseases")) OR ALL=("Periodontal Disease")) OR ALL=("Periodontitis"[Mesh])) OR ALL=("Periodontitis")) OR ALL=("Periodontal Attachment Loss"[Mesh])) OR ALL=("Periodontal Attachment Loss")) OR ALL=("Furcation Defects"[Mesh])) OR ALL=("Furcation Defects")) OR ALL=("Alveolar Bone Loss"[Mesh])) OR ALL=("Alveolar Bone Loss")) OR ALL=("Bone Defects")) OR ALL=("Intrabony Defects")) OR ALL=("Infrabony Defects")
#2	(ALL=("Melatonin"[Mesh])) OR ALL=("Melatonin")
#3	#1 AND #2

Scopus

#1	(TITLE-ABS-KEY ("Periodontal Diseases") OR TITLE-ABS-KEY ("Periodontal Disease") OR TITLE-ABS-KEY ("Periodontitis") OR TITLE-ABS-KEY ("Periodontal Attachment Loss") OR TITLE-ABS-KEY ("Furcation Defects") OR TITLE-ABS-KEY ("Alveolar Bone Loss") OR TITLE-ABS-KEY ("Bone Defects") OR TITLE-ABS-KEY ("Intrabony Defects") OR TITLE-ABS-KEY ("Infrabony Defects"))
#2	TITLE-ABS-KEY ("Melatonin")
#3	#1 AND #2

Embase

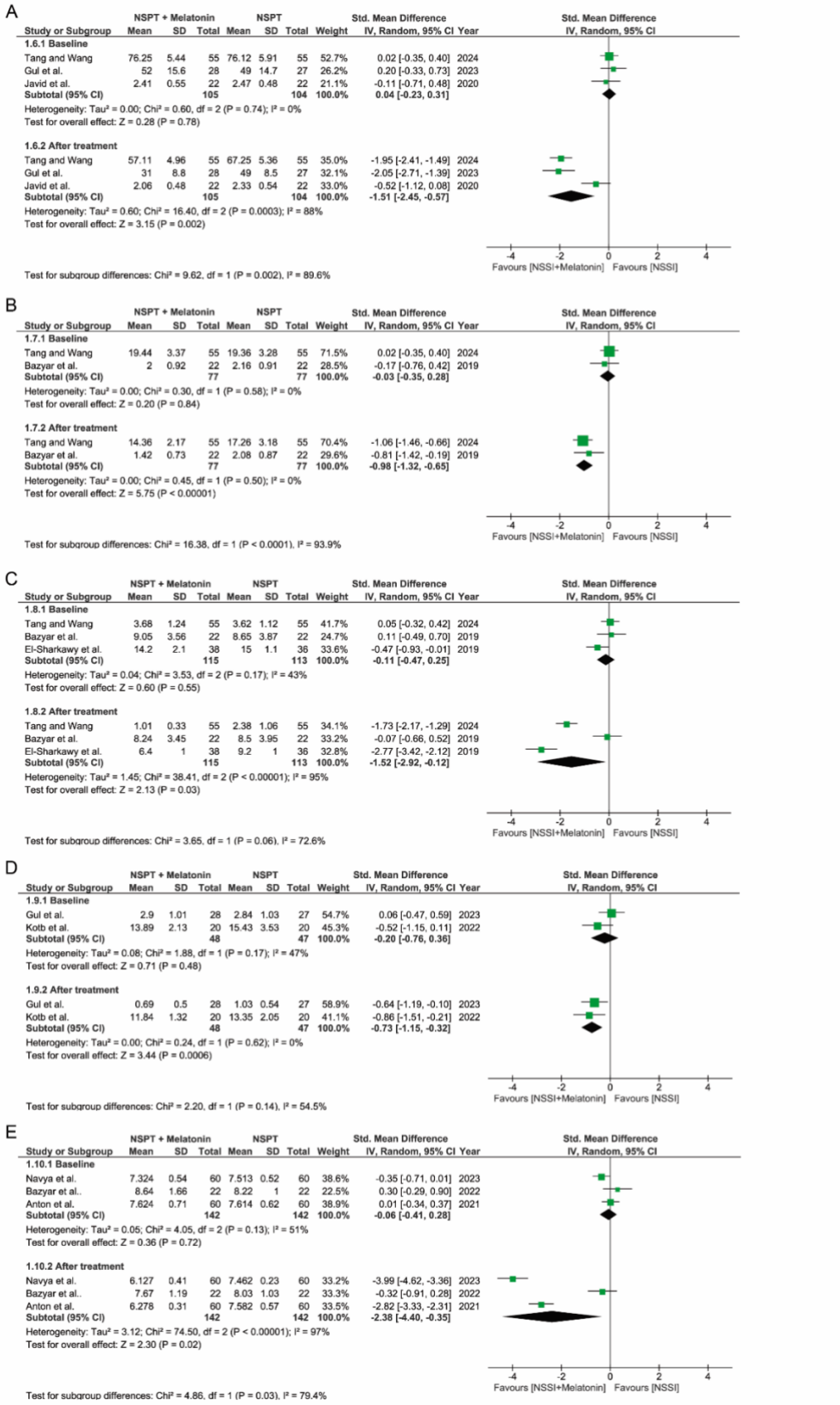
#1	'paradontal disease'/exp OR 'paradontal disease' OR 'periodontal infection'/exp OR 'periodontal infection' OR 'peridontal tissue disease'/exp OR 'peridontal tissue disease' OR 'tooth loss'/exp OR

	'tooth loss' OR 'periodontal diseases'/exp OR 'periodontal diseases' OR 'periodontal disease'/exp OR 'periodontal disease' OR 'periodontitis'/exp OR 'periodontitis' OR 'periodontal attachment loss'/exp OR 'periodontal attachment loss' OR 'furcation defects'/exp OR 'furcation defects' OR 'alveolar bone loss'/exp OR 'alveolar bone loss' OR 'bone defects' OR 'intrabony defects' OR 'infrabony defects'
#2	'5 methoxy n acetyltryptamine'/exp OR '5 methoxy n acetyltryptamine' OR 'melatonin'/exp OR 'melatonin' OR 'melatonina'/exp OR 'melatonina'
#3	#1 AND #2

LILACS

#1	("Periodontal Diseases") OR ("Periodontal Disease") OR ("Periodontitis") OR ("Periodontal Attachment Loss") OR ("Furcation Defects") OR ("Alveolar Bone Loss") OR (“bone defects”) OR (“infrabony defects”) OR (“intrabony defects”)
#2	("Melatonin")

Supplemental File 2. Meta-analysis of biochemical levels of patients treated with melatonin + NSPT in comparison to NSPT; A) IL-1β; B) IL-6; C)TNF-α; D) RANKL; E) HbA1c



Supplemental File 3. Certainty of evidence of each outcome evaluated.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Melatonin	Control	Relative (95% CI)	Absolute (95% CI)	
Probing Depth - Baseline											
12	RCT	not serius	not serious	not serious	serious[b]	none	344	341	-	MD **0.03 lower** (0.13 lower to 0.08 higher)	Moderate
Probing Depth - 2 months											
3	RCT	not serius	not serious	not serious	serious[b]	none	107	107	-	MD **1.8 lower** (2.12 lower to 1.47 lower)	Moderate
Probing Depth - 3 months											
7	RCT	not serius	serius[a]	not serious	serious[b]	none	209	206	-	MD **0.78 lower** (1.27 lower to 0.28 lower)	Low
Probing Depth - 6 months											
5	RCT	not serius	serius[a]	not serious	serious[b]	none	120	117	-	MD **0.64 lower** (1.12 lower to 0.15 lower)	Low
Clinical Attachment Level – Baseline											
10	RCT	not serius	not serious	not serious	serious[b]	none	279	276	-	MD **0.05 lower** (0.12 lower to 0.01 higher)	Low
Clinical Attachment Level - 2 months											
3	RCT	not serius	serius[a]	not serious	serious[b]	none	107	107	-	MD **1.48 lower** (1.74 lower to 1.21 lower)	Low
Clinical Attachment Level - 3 months											
7	RCT	not serius	serius[a]	not serious	serious[b]	none	174	171	-	MD **0.48 lower** (0.83 lower to 0.12 lower)	Low
Clinical Attachment Level - 6 months											
4	RCT	not serius	serius[a]	not serious	serious[b]	none	110	107	-	MD **0.79 lower** (1.3 lower to 0.28 lower)	Low
Gingival Index – Baseline											
6	RCT	not serius	not serious	not serious	serious[b]	none	210	207	-	MD **0** (0.08 lower to 0.07 higher)	Low
Gingival Index - 1 month											
2	RCT	not serius	serius[a]	not serious	serious[b]	none	100	100	-	MD **0.29 lower** (0.47 lower to 0.1 lower)	Low
Gingival Index - 3 months											
6	RCT	not serius	serius[a]	not serious	serious[b]	none	210	207	-	MD **0.3 lower** (0.53 lower to 0.07 lower)	Low
Gingival Index - 6 months											
2	RCT	not serius	not serious	not serious	serious[b]	none	66	63	-	MD **0.1 lower** (0.29 lower to 0.1 higher)	Low
Plaque Index – Baseline											
5	RCT	not serius	not serious	not serious	serious[b]		165	162	-	MD **0.04 higher** (0.05 lower to 0.14 higher)	Moderate

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Melatonin	Control	Relative (95% CI)	Absolute (95% CI)	
Plaque Index - 3 months											
5	RCT	not serius	serius[a]	not serious	serious[b]		165	162	-	MD **0.61 lower** (1.17 lower to 0.06 lower)	Low
Plaque Index - 6 months											
2	RCT	not serius	serius[a]	not serious	serious[b]		66	63	-	MD **0.18 lower** (0.31 lower to 0.05 lower)	Low
BOP – Baseline											
5	RCT	not serius	not serius	not serious	serious[b]		156/173 (90.2%)	151/170 (88.8%)	RR 1.00 (0.97 to 1.03)	**0 fewer per 1.000** (from 27 fewer to 27 more)	Moderate
BOP - 2 months											
3	RCT	not serius	not serius	not serious	serious[b]		38/107 (35.5%)	60/107 (56.1%)	RR 0.68 (0.53 to 0.88)	**179 fewer per 1.000** (from 264 fewer to 67 fewer)	Moderate
BOP - 3 months											
2	RCT	not serius	not serius	not serious	serious[b]		12/66 (18.2%)	16/63 (25.4%)	RR 0.73 (0.38 to 1.38)	**69 fewer per 1.000** (from 157 fewer to 97 more)	Moderate
BOP - 6 months											
2	RCT	not serius	not serius	not serious	serious[b]		11/66 (16.7%)	14/63 (22.2%)	RR 0.76 (0.38 to 1.53)	**53 fewer per 1.000** (from 138 fewer to 118 more)	Moderate
IL-1B – Baseline											
3	RCT	not serius	not serious	not serious	serious[b]		105	104	-	SMD **0.04 higher** (0.23 lower to 0.31 higher)	Moderate
IL-1B - After treatment											
3	RCT	not serius	serius[a]	not serious	serious[b]		105	104	-	SMD **1.51 lower** (2.45 lower to 0.57 lower)	Low
IL-6 – Baseline											
2	RCT	not serius	not serious	not serious	serious[b]		77	77	-	SMD **0.03 lower** (0.35 lower to 0.28 higher)	Moderate
IL-6 - After treatment											
2	RCT	not serius	not serious	not serious	serious[b]		77	77	-	SMD **0.98 lower** (1.32 lower to 0.65 lower)	Moderate
TNF-A – Baseline											
3	RCT	not serius	not serious	not serious	serious[b]		115	113	-	SMD **0.11 lower** (0.47 lower to 0.25 higher)	Moderate
TNF-A - After treatment											
3	RCT	not serius	serius[a]	not serious	serious[b]		115	113	-	SMD **1.52 lower** (2.92 lower to 0.12 lower)	Low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Melatonin	Control	Relative (95% CI)	Absolute (95% CI)	
RANKL – Baseline											
2	RCT	not serius	not serious	not serious	serious[b]		48	47	-	SMD **0.2 lower** (0.76 lower to 0.36 higher)	Moderate
RANKL - After treatment											
2	RCT	not serius	not serious	not serious	serious[b]		48	47	-	SMD **0.73 lower** (1.15 lower to 0.32 lower)	Moderate
HbA1c – Baseline											
3	RCT	not serius	not serious	serious[c]	serious[b]		142	142	-	SMD **0.06 lower** (0.41 lower to 0.28 higher)	Low
HbA1c - After treatment											
3	RCT	not serius	serius[a]	serious[c]	serious[b]		142	142	-	SMD **2.38 lower** (4.4 lower to 0.35 lower)	Very Low

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardised mean difference

a. Higher heterogeneity with no overlapping confidence interval
b. Number of sites evaluated is lower to a better conclusion, below to optimum size information.
b. Limited external applicability. Only patients with type 2 diabetes were included in analysis.

2.2 ARTIGO CIENTÍFICO 2

O artigo científico foi enviado para publicação no periódico Brazilian Journal of Oral Sciences. A estruturação do artigo baseou-se nas instruções aos autores preconizadas pelo periódico (ANEXO 1).

Evaluation of 1% melatonin gel as an adjunctive treatment for periodontitis in individuals with obesity: a clinical case report

ABSTRACT:

Oxidative stress plays a critical role in tissue damage associated with periodontal disease. Obesity has also been identified as a metabolic disorder linked to periodontitis, influencing immune responses and causing an imbalance in cytokine levels. Additionally, melatonin deficiency has been correlated with both obesity and periodontal disease, fostering a pro-inflammatory environment in the body. The anti-inflammatory properties of melatonin may help regulate and mitigate inflammation simultaneously, prompting investigations into the potential effects of exogenous melatonin supplementation in combination with scaling and root planing (SRP) in obese individuals. This study aimed to present the clinical outcomes achieved by using an experimental melatonin gel as an adjunctive therapy to SRP in individuals with obesity and periodontitis. A total of three participants were recruited, and treatments (test and control) were assigned to two eligible sites in a split-mouth model. The experimental group received SRP combined with 1% melatonin gel applied to the periodontal pocket, while the control group underwent SRP with a placebo gel applied to the periodontal pocket. Clinical parameters, including visible plaque index, bleeding on probing, probing depth, and clinical attachment level, were assessed at baseline and three months post-therapy. Improvements in periodontal parameters were observed at the study's conclusion.

Keywords: antimicrobial therapy, non-surgical periodontal therapy, periodontitis, obesity, melatonin.

1. INTRODUCTION

Obesity is recognized as a global epidemic, with World Health Organization (WHO) data indicating that global obesity has nearly tripled since the 1970s. It is estimated that over 1.9 billion adults are overweight, of which more than 650 million are classified as obese (WHO, 2021). In Brazil, data from the National Health Survey (PNS, 2019) reveal that obesity, which includes a subset of individuals with excess weight, affects 25.9% of the population approximately 41.2 million adults. Obesity poses a significant public health challenge, as it substantially increases the risk of cardiovascular diseases, musculoskeletal disorders, diabetes, and certain types of cancer (Blüher M., 2019), impacting individuals' lives and causing millions of deaths annually (Ng *et al.,* 2014).

Specifically, regarding the impact of obesity on oral health, one of the main alterations observed is an increased risk of periodontal diseases (Zhao *et al.,* 2022). A recent systematic review with meta-analysis reported a positive association between obesity and periodontitis, irrespective of age or geographic region (Kim *et al.,*2022). This finding aligns with a meta-review published in 2018, which included 14 systematic review studies and concluded that the synthesis of these works supports obesity as a contributing factor to increased periodontal complications (Suvan *et al.,* 2018). This correlation can be explained by the systemic inflammation triggered by both pathological processes (Virto *et al.,* 2018).

Adipose tissue is a type of connective tissue composed of adipocytes, preadipocytes, fibroblasts, stromal cells, and macrophages (Lee M. *et al.,* 2019; Flehmig G *et al*., 2014). Its functions include energy storage, thermal insulation, and regulation of internal organ function, as well as immune and endocrine systems. Adipose tissue can be categorized into white adipose tissue (WAT), brown, beige/brite, and pink adipose tissue (Lee *et al.,* 2019; Flehmig G. *et al.,* 2014; Cinti, 2018). WAT is further divided into visceral (vWAT) and subcutaneous (sWAT) depots (Lee *et al.,* 2019; Flehmig G. *et al.,* 2014; Cinti, 2018). Visceral WAT is associated with insulin resistance, inflammation, dyslipidemia, obesity, and type 2 diabetes (Zhao *et al.,* 2022; Zorena *et al.,* 2020; Lee *et al.,* 2019; Flehmig G. *et al.,* 2014;

Szewczyk-Golec *et al.,* 2015). Large quantities of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), and plasminogen activator inhibitor-1 (PAI-1) are secreted by adipose tissue and are proportional to increased body mass index (BMI) (Zhao *et al.,* 2022; Nishimura *et al.,* 2001), explaining the link between obesity and periodontal disease.

These adipokines, including TNF-α, IL-6, IL-8, and PAI-1, create a pro-inflammatory environment in the body. Combined with low-grade inflammation caused by gram-negative bacteria and inflammatory mediators (Abu-Shawish *et al.,* 2022; Thomas *et al.,* 2020), this promotes the progression of periodontal disease.

Non-surgical periodontal therapy includes oral hygiene instruction, motivation, and scaling and root planing (SRP), which is considered the gold standard for treating periodontitis (Lu *et al.,* 2021; Sanz *et al.*, 2021; Liu *et al.,* 2022). However, various adjunctive therapies have been proposed to enhance and stabilize clinical outcomes achieved by SRP, with melatonin being one of the most notable. A recent systematic review, including seven studies with a total of 412 participants, concluded that melatonin supplementation improves clinical periodontal parameters following SRP and may be considered a potential adjunctive treatment (Liu *et al.,* 2022).

Melatonin is an indolamine primarily secreted by the pineal gland (Zorena *et al.,* 2020) and produced in gingival tissues and salivary glands (Balaji *et al.,* 2021). This hormone is involved in several functions, including the regulation of biological clocks and energy metabolism, as well as antioxidant and anti-inflammatory activities (Szewczyk-Golec *et al.,* 2015; Lu *et al.,* 2021). Melatonin protects against inflammation and cellular damage caused by reactive oxygen species, has angiogenic properties (Meenakshi *et al.,* 2020), acts as an immunomodulator (Balaji *et al.,* 2021), and reduces adipokine production in visceral WAT (Szewczyk-Golec *et al.,* 2015). Its dual pro- and anti-inflammatory roles allow it to promote, regulate, and neutralize inflammation simultaneously (Ragdona *et al.,* 2010).

Studies have reported lower melatonin levels in individuals with severe periodontitis compared to healthy individuals, sparking interest in the potential effects of exogenous melatonin supplementation following SRP in periodontitis (Balaji *et al.*, 2021; Wang C *et al.*, 2022). Similarly, research suggests a relationship

between obesity and reduced circulating melatonin levels (Szewczyk-Golec *et al.,* 2015; Cipolla-Neto *et al.,* 2014). A recent review proposes a potential role for melatonin in metabolic diseases, such as obesity (Ramirez *et al.,* 2021).

Despite this suggested association between melatonin, obesity, and periodontal disease, only two preclinical studies in rats have investigated this potential correlation. The first study found significantly reduced melatonin levels in obese rats with periodontitis, accompanied by up to a 27.71% increase in alveolar bone loss, deeper periodontal pockets, and a modified gingival index. Histological analyses revealed pronounced destruction of periodontal tissue and heightened osteoclastic activity in obese rats with periodontitis. The authors suggested that melatonin deficiency might be a key mechanism explaining the association between obesity and periodontitis (Virto *et al.,* 2018).

In the second study, melatonin as an adjunctive therapy significantly reduced alveolar bone loss and exerted a protective anti-inflammatory effect in rats affected by the comorbidities of periodontitis and obesity (Virto *et al.,* 2018).

Given the lack of clinical trials evaluating the impact of adjunctive melatonin therapy (1% gel applied locally to the gingival sulcus) in participants with obesity and periodontal disease, this study aimed to present the clinical outcomes achieved using a 1% melatonin gel as an adjunctive treatment to SRP in individuals with obesity and periodontitis through clinical case reports.

2. METHODS

2.1 Ethical Statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, established by the World Medical Association in 1975. It was submitted to and approved by the Research Ethics Committee of the Federal University of Juiz de Fora (CAAE: 75906323.3.0000.5147). Additionally, the study adhered to the guidelines established by the Consolidated Standards for Reporting Trials (CONSORT). Participants were required to read, understand, and sign a

written informed consent form (in duplicate) and demonstrate their willingness and ability to adhere to the study's visit schedule.

2.2 Population

Five participants (2 females, 3 males), aged between 50 and 62 years, all with obesity (BMI > 30 kg/m²) and stage III or IV periodontitis, were recruited for the study.

Inclusion criteria were adults over 18 years of age, of both sexes, with obesity (BMI > 30 kg/m²), and diagnosed with stage III or IV periodontitis (Papanou *et al.,* 2018; Caton *et al.,* 2018). Eligible participants had a minimum of two non-adjacent sites in distinct teeth with a clinical attachment loss of at least 5 mm, without mobility or furcation involvement (Pilloni *et al.,* 2023). Candidates were excluded if they had a history of trauma or congenital deformities, and only teeth that were vital and without endodontic lesions were included.

Exclusion criteria included individuals with allergies to any component of the proposed formulation, those who had undergone periodontal therapy in the past six months, smokers, pregnant or lactating women, and individuals who had used anti-inflammatory drugs or antibiotics chronically in the three months prior to the study. Also excluded were participants who had received chemotherapy or radiotherapy in the past five years or those with uncontrolled systemic diseases.

2.3 Clinical Evaluation

As a triple-blind study, random allocation sequence generation and assignment of participants to interventions were performed by an investigator separate from the clinical examiner and operator administering the treatment. The participants, the operator, and the clinical examiner were blinded to the pre-determined group assignments.

Participants underwent a comprehensive periodontal examination at six sites per tooth, excluding third molars, performed by a single calibrated and blinded

examiner. The clinical parameters assessed included visible plaque index (VPI), bleeding on probing (BOP), probing depth (PD), and clinical attachment level (CAL).

The VPI was calculated as the number of surfaces with visible plaque divided by the total number of surfaces examined, following air-drying of the dental surfaces, across six surfaces per tooth (Ainamo and Bay, 1975). BOP was recorded as bleeding occurring within 30 seconds of probing. PD was measured as the distance from the gingival margin to the base of the gingival sulcus, and CAL as the distance from the cementoenamel junction (CEJ) to the base of the pocket.

All assessments were performed at baseline and after treatment with non-surgical subgingival instrumentation (NSSI), with or without adjunctive 1% melatonin therapy. Follow-up evaluations were conducted at 3- and 6-months post-treatment.

2.4 SRP and Adjunctive Treatment

Patients received oral hygiene instructions and underwent SRP (Sanz *et al.,* 2020), which included supra- and subgingival debridement under local anesthesia across all four quadrants. The procedure utilized ultrasonic and manual instruments (Gracey curettes, McCall instruments, and Hirschfield files, as necessary).

As this was a split-mouth study, one side (left or right) or one quadrant (1:3 / 2:4) received the experimental adjunctive treatment, while the opposite side/quadrant received a placebo. In the experimental group, a 1% melatonin gel was applied into the periodontal pockets using a syringe with a specialized cannula immediately following SRP in all teeth (Fig. 1).

The experimental melatonin gel was formulated based on the protocol described by Gonde et al. (2022) and prepared by a compounding pharmacy (A BOTICA - Farmácia de Manipulação, Governador Valadares, MG, Brazil). The formulation involved dissolving propylene glycol in distilled water in a 1:4 ratio, followed by stirring. Methylparaben and propylparaben were added as preservatives, and the solution was sonicated for 30 minutes. Carbopol 934P (1%) was then dispersed into the solution. After 24 hours, 1 g of raw melatonin powder was added

and thoroughly mixed. The final gel was prepared by incorporating triethanolamine (Gonde *et al.,* 2022).

On the opposite side, the SRP treatment was identical, but a placebo gel was used (Fig. 2). The placebo gel consisted of propylene glycol dissolved in distilled water in a 1:4 ratio, followed by stirring. Methylparaben and propylparaben were added, and the solution was sonicated for 30 minutes. Carbopol 934P (1%) was then dispersed, and the gel was finalized with the addition of triethanolamine.

To prevent gel displacement or dissolution in the oral environment, a periodontal surgical dressing (Coe-Pak, GC Company) was applied immediately after subgingival gel application, limited to the treated region. Participants were instructed to avoid excessive chewing, sticky foods, vigorous brushing near the treated areas, or the use of interdental devices for at least one week (Gonde *et al.,* 2022). During this period, participants were advised to use a 0.12% chlorhexidine solution, applied with sterile gauze, to control biofilm twice daily for seven days.

The treatments were conducted at the nighttime clinics of the UFJF Advanced Campus in Governador Valadares between June and December 2024. In this case series, three participants successfully completed the described protocol.

Fig. 1: Syringe used for gel application.

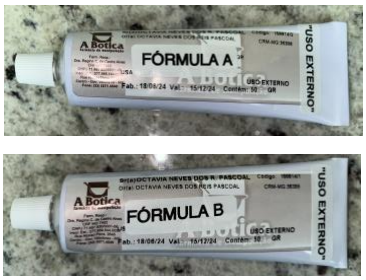


Fig. 2: Experimental melatonin gel.

3. RESULTS

The clinical parameter results at baseline and 3 months post-treatment are presented in Table 1. Postoperative healing occurred without complications in all

patients, and no adverse reactions (either local or systemic) were observed in any of the study groups, indicating the biocompatibility of the 1% melatonin gel.

Both treatment sites exhibited reductions in probing depth (PD) and improvements in clinical attachment level (CAL) 3 months after the treatment. However, the SRP + MEL group demonstrated a greater reduction in PD, from 6.7 ± 0.8 mm to 3.8 ± 1.09 mm, compared to the SRP + PLACEBO group, which showed a reduction from 6.7 ± 1.0 mm to 4.7 ± 2.1 mm. Lower PD values were observed in the experimental group (Table 1). Regarding CAL, the experimental group showed a gain from 5.7 ± 1.8 mm to 3.3 ± 1.9 mm, while the control group showed a gain from 6.2 ± 1.0 mm to 3.7 ± 2.1 mm, with better CAL outcomes in the experimental group. (Table 2)

Table 1. Mean and standard deviation of probing depth (PD) at baseline and after 3 months.

PROBING DEPTH (PD)							
SRP + MELATONIN				SRP + PLACEBO			
		BASELINE	3 MONTHS			BASELINE	3 MONTHS
PARTICIPANT 1	SITE 1	7	3	PARTICIPANT 1	SITE 1	7	2
	SITE 2	5	2		SITE 2	5	3
PARTICIPANT 2	SITE 1	7	2	PARTICIPANT 2	SITE 1	7	5
	SITE 2	7	5		SITE 2	6	5
PARTICIPANT 3	SITE 1	7	4	PARTICIPANT 3	SITE 1	7	5
	SITE 2	7	7		SITE 2	8	8
	MEAN	**6,7**	**3,8**		**MEAN**	**6,7**	**4,7**
	STANDARD DEVIATION	**0,8**	**1,9**		**STANDARD DEVIATION**	**1,0**	**2,1**

In terms of VPI (table 3) and BOP (table 4), the test sites showed a reduction in scores 3 months after treatment, while no significant changes were observed in the control group.

CLINICAL ATTACHEMENT LEVEL							
SRP + MELATONIN				SRP + PLACEBO			
		BASELINE	3 MONTHS			BASELINE	3 MONTHS
PARTICIPANT 1	SITE 1	5	4	PARTICIPANT 1	SITE 1	5	0
	SITE 2	4	1		SITE 2	6	4
PARTICIPANT 2	SITE 1	9	5	PARTICIPANT 2	SITE 1	6	3
	SITE 2	6	5		SITE 2	8	4
PARTICIPANT 3	SITE 1	5	1	PARTICIPANT 3	SITE 1	6	5
	SITE 2	5	4		SITE 2	6	6
	MEAN	**5,7**	**3,3**		**MEAN**	**6,2**	**3,7**
	STANDARD DEVIATION	**1,8**	**1,9**		**STANDARD DEVIATION**	**1,0**	**2,1**

Table 2: Mean and standard deviation of Clinical Attachment Level (CAL) at baseline and after 3 months.)

VISIBLE PLAQUE INDEX							
SRP + MELATONIN				SRP + PLACEBO			
		BASELINE	3 MONTHS			BASELINE	3 MONTHS
PARTICIPANT 1	SITE 1	0	0	PARTICIPANT 1	SITE 1	0	0
	SITE 2	1	0		SITE 2	1	0
PARTICIPANT 2	SITE 1	0	1	PARTICIPANT 2	SITE 1	0	1
	SITE 2	1	1		SITE 2	1	1
PARTICIPANT 3	SITE 1	1	0	PARTICIPANT 3	SITE 1	0	0
	SITE 2	1	1		SITE 2	0	0
	MEAN	**0,7**	**0,5**		**MEAN**	**0,3**	**0,3**
	STANDARD DEVIATION	**0,5**	**0,5**		**STANDARD DEVIATION**	**0,5**	**0,5**

Table 3. Mean and standard deviation of Visible Plaque Index (VPI) at baseline and after 3 months.)

BLEEDING ON PROBING							
SRP + MELATONIN				SRP + PLACEBO			
		BASELINE	3 MONTHS			BASELINE	3 MONTHS
PARTICIPANT 1	SITE 1	1	0	PARTICIPANT 1	SITE 1	1	1
	SITE 2	1	0		SITE 2	1	1
PARTICIPANT 2	SITE 1	1	0	PARTICIPANT 2	SITE 1	1	1
	SITE 2	1	0		SITE 2	1	0

PARTICIPANT 3	SITE 1	1	0	PARTICIPANT 3	SITE 1	0	0
	SITE 2	1	0		SITE 2	1	1
	MEAN	**1,0**	**0,0**		**MEAN**	**0,8**	**0,7**
	STANDARD DEVIATION	**0,0**	**0,0**		**STANDARD DEVIATION**	**0,4**	**0,5**

(table 4: Mean and standard deviation of Bleeding on Probing (BOP) at baseline and after 3 months.)

4. DISCUSSION

The primary goal of periodontal therapy is the regeneration of tissues damaged by the inflammatory cascade caused by periodontal disease. Obese individuals may experience worsening of periodontitis due to altered levels of pro-inflammatory cytokines in their plasma, which impacts the immune response (Abu-Shawish *et al.,* 2022; Zorena *et al.,* 2020). Virto *et al.,* 2018) explains that this correlation arises from the systemic inflammation triggered by both obesity and periodontal disease.

Obese individuals have lower circulating melatonin levels (Szewczyk-Golec *et al.,* 2015; Cipolla-Neto *et al.,* 2014), and melatonin levels in those with severe periodontitis are also lower than in healthy individuals (Balaji *et al.,* 2021; Wang *et al.,* 2022). Based on this, the aim of this study was to present clinical results of using a 1% melatonin gel as an adjunctive treatment to scaling and root planing (SRP) in individuals with obesity and periodontitis.

No adverse reactions (local or systemic) were observed in any of the study groups, suggesting that the 1% melatonin gel is biocompatible. To date, there are no reports in the literature of adverse reactions to melatonin when used topically or systemically as an adjunct in periodontal therapy. The satisfactory healing observed in this study aligns with the findings of Ahmed *et al.,* 2021.

Regarding probing depth (PD), the melatonin group showed an average reduction of 0.9 mm compared to the control group, which is a clinically relevant finding. Better PD outcomes in the experimental group were also observed in studies

by Gonde *et al.,* 2022, El-Sharkawy *et al.,* 2019, and Chitsazi *et al.,* 2017, with statistically significant results. This contrasts with the studies by Sarac Gul *et al.,* 2024, Ahmed *et al.,* 2021, Faramarzi *et al.,* 2021, and Tinto *et al.,* 2020, which found significant changes within groups from baseline to post-treatment, but no statistically significant differences between the test and control groups.

As for clinical attachment level (CAL), both groups showed improvements when comparing baseline and post-treatment values. However, no clinically significant differences were found when comparing the melatonin and placebo groups, which aligns with the results of Ahmed *et al.,* 2021, Faramarzi *et al.,* 2021, and Tinto *et al.,* 2020. On the other hand, the studies by Gonde *et al.,* 2022, El-Sharkawy *et al.,* 2019, and Chitsazi *et al.,* 2017 showed statistically significant improvements in CAL in the melatonin group compared to the placebo group. The absence of this effect in our study may be due to the small sample size.

The clinical improvements in periodontal parameters in our study are consistent with those reported by Virto *et al.,* 2018, where melatonin as an adjunctive therapy contributed to significant reduction of alveolar bone loss, providing a protective anti-inflammatory effect in rats with both periodontitis and obesity. This anti-inflammatory effect of melatonin was also noted by Lu *et al.,* 2021.

Although both VPI (Visible Plaque Index) and BOP (Bleeding on Probing) showed improvement in both groups at 3 months, there were no significant differences between the groups, as observed in studies by Sarac Gul *et al.,* 2024, Paladugu *et al.,* 2023, Anton *et al.,* 2021, and Bazyar *et al.,* 2019.

While several studies recommend the use of melatonin in dentistry (Sarac Gul *et al.,* 2024, Paladugu *et al.,* 2023; Gonde *et al.,* 2022; Anton *et al.,* 2021; Ahmed *et al.,* 2021; Faramarzi *et al.,* 2021; Tinto *et al.,* 2020; El-Sharkawy *et al.,* 2019; Bazyar *et al.,* 2019; Chitsazi *et al.,* 2017), there are still unanswered questions, such as its antimicrobial effects, mechanism of action, and the most effective administration route (local vs. systemic).

The small sample size and short follow-up period were limitations of this study. Future clinical trials with larger sample sizes and longer follow-up periods are

recommended to better assess the efficacy of melatonin as an adjunctive therapy to SRP in individuals with periodontitis and obesity.

5. CONCLUSION

Despite the limitations of this study, improvements in periodontal parameters were observed after the experimental therapy, suggesting that 1% melatonin applied via the gingival sulcus may be an effective treatment for periodontitis. Its beneficial effects may be even more significant in patients with systemic conditions, such as obesity.

Although some studies recommend the use of melatonin for periodontitis treatment, there are still several gaps that need to be addressed, such as its antimicrobial effects, mechanism of action, and the most appropriate route of administration (local vs. systemic).

Given the absence of clinical trials assessing the impact of adjunctive melatonin therapy (1% local/gingival sulcus) in individuals with obesity and periodontal disease, further studies are necessary to explore this relationship through randomized clinical trials.

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CONCLUSÃO

Dentro das limitações deste estudo, foi possível observar uma melhora significativa nos parâmetros periodontais após a terapia experimental, indicando que a melatonina (1% via sulco gengival) pode ser um medicamento eficaz no tratamento da periodontite. Seus efeitos benéficos parecem ser ainda mais relevantes em pacientes com patologias sistêmicas, como obesidade, condição que está associada a uma inflamação sistêmica crônica mediada por altos níveis de adipocinas pró-inflamatórias (TNF-α, IL-6, IL-8 e PAI-1) e agravada pela presença de bactérias gram-negativas e mediadores inflamatórios.

Nossa revisão sistemática e meta-análise revelou que o uso de melatonina na TPNC proporciona benefícios clínicos e bioquímicos significativos. Foram observadas melhorias notáveis nos parâmetros clínicos, como profundidade de sondagem (PS), nível de inserção clínica (NIC), índice gengival (IG) e índice de placa (IP). A melatonina também reduziu significativamente os biomarcadores pró-inflamatórios (IL-1β, IL-6, TNF-α), RANKL e os níveis de HbA1c, indicando potenciais benefícios sistêmicos. No entanto, a certeza das evidências variou de baixa a moderada.

De acordo com a literatura consultada, conclui-se que existe uma associação positiva entre a obesidade e a doença periodontal onde essa correlação pode ser explicada pela inflamação sistêmica desencadeada por ambos os processos patológicos. Grandes quantidades de adipocinas (TNF-α, IL6, IL8 e PAI-1) são secretadas pelo tecido adiposo; e isso associado a inflamação de baixo grau devido a bactérias gram-negativas e os mediadores inflamatórios influenciam na progressão da doença periodontal.

A melatonina protege contra a inflamação e diminui a produção de adipocinas pelo tecido adiposo; podendo promover, regular e neutralizar a inflamação simultaneamente; alguns trabalhos demostraram que indivíduos com doença periodontal apresentam níveis de melatonina menores quando comparados com indivíduos saudáveis, no mesmo sentido a obesidade também está relacionada a uma deficiência dos níveis de melatonina circulantes.

A TPNC é um dos principais tratamentos para a periodontite, porém várias terapias adjuvantes vem sendo consideras, entre elas a suplementação de melatonina. Apesar de alguns estudos recomendarem o uso de melatonina no tratamento da periodontite, ressaltamos que diante da ausência de ensaios clínicos avaliando o impacto da terapia adjuvante com melatonina (1% via local/sulco gengival) em indivíduos com obesidade e doença periodontal; portanto, são recomendados estudos adicionais de alta qualidade, focados em métodos de administração, dosagens e períodos de tratamento, para confirmar esses achados e avaliar os efeitos de longo prazo da melatonina na terapia periodontal.

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ANEXO A

Normas para submissão do artigo referente ao capítulo 1 na revista Journal of Periodontal Research, podem ser encontradas no link: https://onlinelibrary.wiley.com/page/journal/16000765/homepage/forauthors.html

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