

Review Article

A systematic review on the role of ozone therapy in periodontitis

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Abstract

Bacterial infection triggers periodontitis, which is a long-standing inflammatory disease of the oral cavity that damages the tissues supporting the teeth. Ozone therapy, known for its antimicrobial, anti-inflammatory, and biostimulatory effects, has been applied as an adjunct in periodontal treatment. This review evaluates its efficacy in lowering inflammatory markers, including matrix metalloproteinase-8 (MMP-8), interleukin-1 beta (IL-1 β), and tumor necrosis factor-alpha (TNF- α) and its potential to enhance the repair of periodontal tissues. A thorough search of major bibliographic databases, such as PubMed, Scopus, and Google Scholar, was carried out. Studies investigating alterations in inflammatory biomarkers among patients receiving ozone therapy for periodontitis, which examined both before and after the interventions, were considered for inclusion. Data extraction emphasized both the levels of these biomarkers and clinical measures reflecting periodontal recovery. The review indicates that ozone therapy significantly reduces inflammatory biomarkers, particularly MMP-8, IL-1 β , and TNF- α , inhibits periodontal tissue degradation, and promotes healing by modulating both microbial activity and host response. Ozone therapy shows promise as an adjunctive treatment for periodontitis by reducing inflammation and supporting tissue repair. However, additional randomized clinical trials are warranted to confirm its long-term efficacy and the standardization of treatment protocols.

Keywords: Ozone therapy, Periodontitis, Inflammatory biomarkers, Periodontal healing

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INTRODUCTION

The body's immune reaction to bacterial infections in the oral cavity results in periodontitis, a chronic inflammatory disease marked by gingival inflammation, periodontal ligament deterioration and alveolar bone resorption develop due to the body's immunological reaction to bacteria localized within the mouth. With disease progression,

deterioration of the supporting periodontal structures causes teeth to become loose and may ultimately result in tooth loss, involving the alveolar bone and periodontal ligament. Periodontitis progresses through several stages, ranging from initial gingival inflammation (Stage I) to moderate (Stage II) and severe destruction of periodontal tissues (Stage III – IV) which ultimately result in tooth mobility and loss.

Recognizing these stages is crucial for diagnosis and treatment planning [1,2].

Inflammatory molecules such as interleukin-1 beta (IL-1 β) and tumor necrosis factor-alpha (TNF α) play key roles in tissue degradation, contributing to the loss of periodontal support [4]. Matrix metalloproteinase-8 (MMP-8), the primary enzyme responsible for breaking down collagen in the extracellular matrix, is also elevated in periodontitis patients [7]. Elevated levels of these biomarkers reflect the progression of periodontal inflammation and tissue destruction, including resorption of alveolar bone, deterioration of gingival tissues, and weakening of the ligamentous structures that anchor the teeth [3,4].

In recent decades, ozone therapy has emerged as an adjunctive treatment for periodontitis. Medical-grade ozone (O₃), a triatomic oxygen molecule, exhibits strong antimicrobial, anti-inflammatory, and biostimulatory properties [5,6]. It can be administered in gaseous form, as ozonated water, or in ozonated oil, which are produced using ozone generators that convert medical oxygen into ozone for safe clinical use. Its antibacterial properties help reduce harmful periodontal pathogens, including *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, while its anti-inflammatory effects can suppress overactive immune responses and accelerate regeneration of periodontal tissues [5,6].

Several clinical studies have demonstrated that ozone therapy can effectively lower levels of key inflammatory biomarkers in periodontitis patients. Nardi *et al* [7] reported a significant reduction in salivary MMP-8 in patients treated with ozonated olive oil mouthwash, and Eltas *et al* [8] observed decreases in IL-1 β and TNF- α following non-surgical periodontal therapy with ozone. These findings indicate that ozone therapy not only inhibits tissue degradation but also promotes periodontal healing, supporting its role as a safe and effective adjunct to conventional periodontal treatment.

The present review examines the role of ozone therapy in the treatment of periodontitis. Highlighting its impact on inflammatory biomarkers pre- and post-therapy. The results of this review are expected to be used as a foundation for developing more effective and scientifically validated periodontal care practices [7].

METHODS

Following PRISMA guidelines, a systematic review was performed. Studies of interest were retrieved from key databases, including PubMed, Scopus, and Google Scholar, examining the effects of ozone therapy on periodontitis and associated changes in inflammatory markers before and after intervention [9,10].

Inclusion criteria

Clinical studies evaluating changes in inflammatory biomarkers after ozone therapy in patients with periodontitis [11], articles published in Scopus or PubMed-indexed journals in the last 10 years [12], and studies that employed clinical metrics as markers of treatment efficacy, such as diminution of clinical attachment, plaque index and probing depth, were compiled [13].

Exclusion criteria

Studies that did not evaluate changes in inflammatory biomarkers [14] and articles that only discuss ozone therapy with no correlation with the cure of periodontitis [15].

RESULTS

Among patients with post-COVID asthenic syndrome, Soldatenko *et al* [22] reported significant reductions in TNF α , IL-1 β , and IL-6 levels with systemic ozone therapy. Compiled clinical studies on ozone therapy are summarised in Table 1 to Table 3. Table 1 reports ozone therapy in systemic and musculoskeletal diseases, while Table 2 is a compilation of ozone therapy in periodontal and peri-implant diseases. Table 3, on the other hand, is a compilation of preclinical studies on ozone therapy in animal models.

DISCUSSION

Based on the results of the analyzed studies, ozone therapy shows significant effectiveness in the treatment of periodontitis, particularly in lowering levels of inflammatory indicators like MMP-8, facilitating accelerated periodontal tissue repair and reducing inflammation. Ozone therapy has increasingly been recognized as a potential adjunct or alternative to standard periodontal treatments, including chlorhexidine, for managing periodontal disease [25,28].

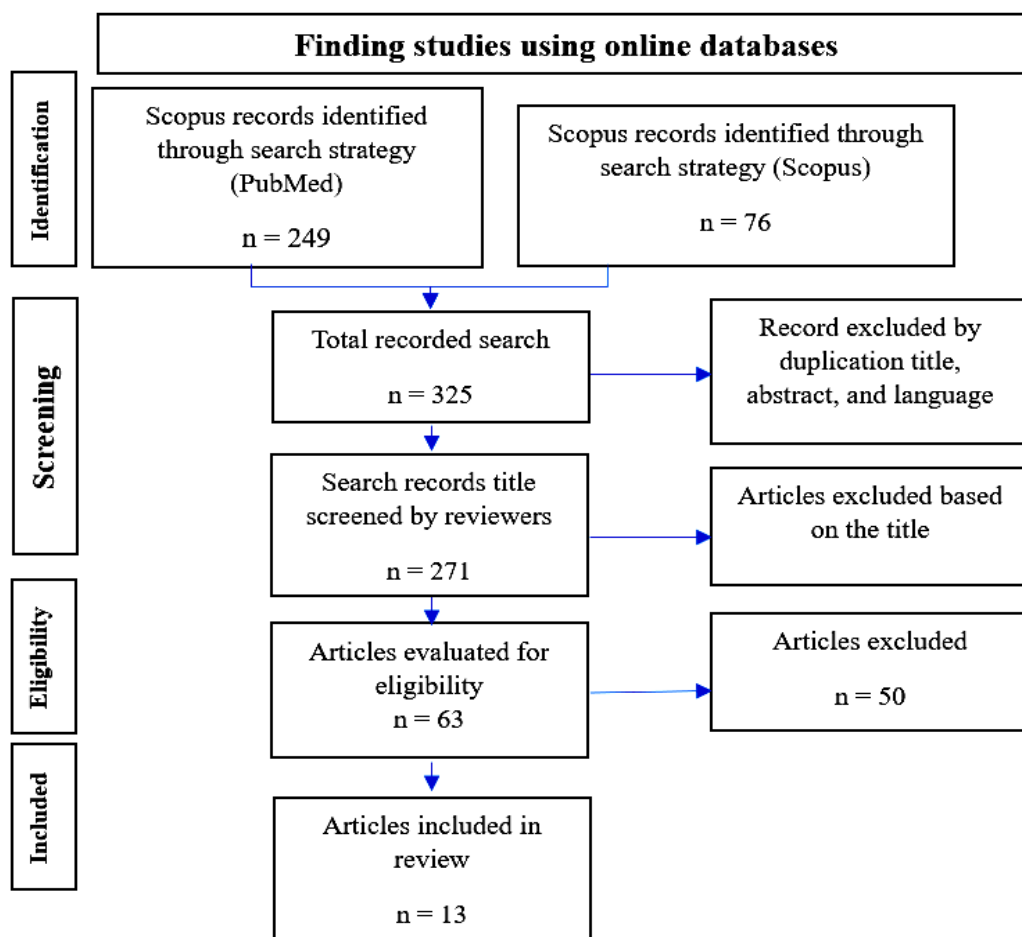


Figure 1: PRISMA 2009 flow diagram identification of studies via online databases

Table 1: Clinical studies on ozone therapy in systemic and musculoskeletal diseases

Reference	Year	Type of study	Methods	Result	Remark
[16]	2024	Observational single-center study	The study compared two groups of patients with diabetic foot ulcers (DFUs): one with neuropathic ulcers and one with ischemic ulcers. Evaluation was performed with digital planimetry and visual analogue scale (VAS) for pain.	Ozone therapy reduced wound size more significantly in patients with neuropathic DFUs than in ischemic DFUs ($p < 0.001$).	Ozone therapy has shown greater effectiveness in accelerating the healing of neuropathic wounds than ischemic wounds.
[17]	2024	Analytical single-center study	A total of 40 individuals experiencing chronic radicular pain were allocated randomly into two treatment groups, one of which received transforaminal epidural steroid injections along with ozone therapy, and one without ozone. Both before and after treatment, the Oswestry Disability Index (ODI) and the Pain Rating Scale (NRS) were used to measure pain.	The two groups did not differ substantially regarding long-term pain relief.	Ozone did not provide a significant additional effect on pain reduction.
[18]	2023	Single-center randomized controlled trial (RCT), parallel-group	60 patients with type 2 diabetes were randomized into two groups: one received systemic ozone therapy, and the other received only standard therapy.	Ozone therapy lowered the latency of P100 waves, showing improvement in impulse conduction in the visual pathway.	Ozone provided benefits in improving the visual pathways in diabetic patients, although it did not directly correlate with glycated hemoglobin (HbA1c) levels.
[19]	2025	Double-blind randomized controlled Trial (RCT)	A total of 59 individuals diagnosed with knee osteoarthritis were randomly divided into three treatment groups. The first group was administered ozone at a concentration of 40 µg/mL, the second group received oxygen as a control, and the third group underwent ozone therapy at 20 µg/mL. Clinical outcomes were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Visual Analogue Scale VAS scores, and standardized functional performance tests.	Ozone delivered intra-articularly at 20 µg/mL and 40 µg/mL concentrations significantly alleviated pain levels and enhanced mobility relative to the control group ($p < 0.05$).	Comparisons between the 20 µg/mL and 40 µg/mL intra-articular ozone doses revealed no significant differences in terms of pain relief and functional mobility enhancement.
[22]	2024	Randomized controlled trial (RCT), single-center	140 patients with post-COVID asthenic syndrome (PCAS) were divided into two groups: (a) Standard drug therapy, (b) Drug therapy + systemic ozone therapy. The evaluation comprised quantification of tumor necrosis factor-alpha, interleukin-1 beta (IL-1β), interleukin-6 (IL-6) levels, together with assessments of cognitive and psychological parameters using the Multidimensional Fatigue Inventory-20 (MFI-20), Montreal Cognitive Assessment (MoCa), insomnia severity index (ISI), Hamilton anxiety rating scale (HARS), clinical global impression – severity (CGI-S) scales.	Compared with the control group, the ozone treated groups exhibited a significant reduction in TNFα ($p = 0.003$), IL1β ($p = 0.022$), and IL6 ($p = 0.012$) levels were significantly decreased, and their mental health ratings increased.	94.2% of patients in the ozone therapy group experienced a full recovery from PCAS, compared to 62.9% in the control group.

Table 2: Clinical studies on ozone therapy in periodontal and peri-implant diseases

Name	Year	Study type	Methods	Result	Remark
[23]	2023	randomized controlled trial (RCT), split-mouth study design	1. Participants: 30 patients with bilateral periodontitis. 2. Intervention: The control group's teeth received chlorhexidine gel, whereas the test group received ozonized gel for two weeks following mechanical debridement without surgery. 3. Evaluation of patients n was carried out at the first, second, and sixth months. This evaluation was focused on monitoring the Plaque Control Record and assessing clinical parameters, including Bleeding on Probing, Probing Pocket Depth, and Clinical Attachment Loss.	Clinical Attachment Loss, Probing Pocket Depth, Bleeding on Probing, and Plaque Control Record were all significantly reduced in both groups ($p < 0.05$); however, no significant differences were detected between the groups.	When treating periodontitis, ozone can be a useful substitute for chlorhexidine.
[24]	2024	Randomized controlled trial (RCT), parallel-group study	1. Participants: 90 patients with stage II-IV periodontitis 2. Intervention: • The test group received ozone gas therapy at a concentration of 2100 parts per million, applied to each site for 60 seconds once a week over a span of four consecutive weeks. • The control group underwent only non-surgical periodontal therapy. Evaluation: Clinical parameters, including Probing Depth (PD), Clinical Attachment Loss (CAL), Plaque Index (PI), and Gingival Index (GI), together with salivary oxidative stress markers such as Malondialdehyde (MDA), Total Antioxidant Capacity (TAC), and Superoxide Dismutase (SOD), were evaluated at the third and sixth months of the study.	Relative to the control group, the test group demonstrated significant elevations in Total Antioxidant Capacity ($p = 0.002$), decreases in Malondialdehyde levels ($p = 0.001$), and increased Superoxide Dismutase activity ($p < 0.001$).	Ozone therapy reduces oxidative stress and promotes periodontal healing, especially in stage III-IV periodontitis.
[25]	2020	Prospective randomized controlled clinical trial (RCT)	1. A total of ninety participants diagnosed with moderate to severe periodontitis enrolled in the study. 2. Interventions: • Group A received a combination of scaling and root planing (SRP) along with ozone gas therapy. • Group B received only scaling and root planing (SRP) treatment. Evaluation: CAL, PPD, and BoP were measured in the 3rd and 6th months.	Versus control group, the ozone therapy group showed significant enhancements in Clinical Attachment Loss (CAL), Probing Pocket Depth (PPD), and Bleeding on Probing (BoP; $p < 0.0001$).	SRP with ozone therapy provides better results than SRP alone in reducing periodontal inflammation.
[26]	2022	Randomized controlled trial (RCT), split-mouth study	1. Participants: 30 patients with 240 pathological periodontal sites. 2. Interventions: a. Ozone Group: Ozonized water is given after SRP. b. PBM group: Given photo bio modulation (PBM) after SRP. Evaluation: PPD, PI, and BoP measured from 1st to 6th months.	PBM was more effective in lowering PPD than ozone after the 5th and 6th months ($p < 0.05$).	Ozone and PBM are both effective as adjunct therapies for SRPs, but PBMs are superior in the long term.
[27]	2023	Randomized controlled trial (RCT)	1. Participants: 60 patients with peri-implant mucositis. 2. Interventions: 2. Ozone Group: Ozonized hydrogel. Control Group: Chlorhexidine was given 1% gel. Evaluation of periodontal parameters, including Bleeding on Probing (BoP), Probing Pocket Depth (PPD), and Plaque Index (PI), was conducted at the first and third months.	Both groups experienced significant declines in BoP and PPD ($p < 0.05$), with significant intergroup differences observed at specific time points.	Ozone and chlorhexidine are equally effective in reducing peri-implant mucositis.
[7]	2020	Randomized controlled trial (RCT)	1. Participants: 50 patients with periodontitis. 2. Interventions: a. Group A: Scaling and Root Planning (SRP) + ozonated olive oil mouthwash. b. Group B: SRP only. Evaluation: MMP-8, PI, BoP, and PPD were measured during the first, third, and sixth months.	Both groups showed significant reductions in Bleeding on Probing (BoP) and Probing Pocket Depth (PPD; $p < 0.05$), with notable differences between groups.	Ozonated olive oil mouthwash helps lower periodontal inflammation more effectively than SRP alone.

Table 3: Preclinical studies on ozone therapy in animal models

Name	Year	Type of study	Method	Result	Remark
[20]	2024	Randomized controlled trial (RCT) in an animal model (rats)	Mice with sciatic nerve injuries were divided into four groups: 1. Control (no injury) 2. Injuries without therapy 3. Perineural ozone therapy Intraperitoneal ozone therapy Evaluation was carried out using functional tests (pinch test, rotarod test), histological analysis, and toluidine blue staining.	1. The ozone therapy group showed increased nerve regeneration compared to the group without therapy. 2. Improvement was more significant in the intraperitoneal than the perineural ozone therapy group.	Intraperitoneal ozone therapy is more effective in reducing myelin degeneration and promoting nerve regeneration than perineural therapy.
[21]	2024	Randomized controlled trial (RCT) in an animal model (rats)	120 mice were divided into 5 groups with different treatments: 1. Saline solution 2. Sunflower oil 3. Ozonized sunflower oil 4. Ozone bagging: a topical ozone therapy method in which the wound area is enclosed in a plastic bag and exposed to ozone gas to enhance oxygenation, provide antimicrobial effects, and accelerate tissue regeneration. 5. Combination of ozonization sunflower oil + ozone bagging. Wound evaluation was carried out by macroscopic, histopathology, and measurement of the tensile strength of the wound tissue.	By the seventh postoperative day, compared with the other groups, the ozone bagging group showed an increased rate of wound contraction.	Ozone bagging was more effective than other methods in accelerating wound healing in mice.

Multiple studies have shown that ozone therapy, when combined with scaling and root planing (SRP), a non-surgical approach for treating periodontitis, can be beneficial and improve clinical outcomes more effectively than SRP alone. Furthermore, studies evaluating ozone therapy in comparison with chlorhexidine for the treatment of periodontitis have demonstrated that both interventions are similarly effective in alleviating inflammation of the periodontal tissues, controlling gingival bleeding during probing, and reducing the depth of periodontal pockets. However, since ozone exhibits fewer adverse effects than chlorhexidine, such as tooth discoloration and soft tissue irritation, its use is recommended [29,30].

Moreover, studies have shown that ozone therapy, administered as an ozonated olive oil mouthwash, is helpful in reducing the levels of inflammatory biomarkers like MMP-8 in the saliva of individuals with periodontitis. Ozone may help lessen the deterioration of periodontal tissue and slow the course of illness, according to this drop in MMP-8 levels. Studies that looked at how ozone affected oxidative stress in saliva also found similar outcomes, with ozone therapy increasing total antioxidant capacity (TAC) and lowering levels of malondialdehyde (MDA), a sign of oxidative stress [31,32]. Ozone therapy has shown beneficial effects not only in managing periodontitis but also in treating peri-implant mucositis, an inflammatory condition that occurs around dental implants [27,33]. According to studies, ozonized hydrogel is just as effective as chlorhexidine at lowering inflammation and enhancing the health of the peri-implant mucosa, making it a safer substitute with fewer adverse effects [26,34].

Furthermore, studies have also shown that ozone therapy has a positive impact on patients with type 2 diabetes who experience periodontitis. Clinical studies indicate that combining ozone therapy with SRP can significantly reduce glycated hemoglobin (HbA1c) levels compared to SRP alone. These results indicate that ozone therapy may not only improve periodontal health but also support better glycemic control in diabetic patients, who are at higher risk for developing periodontal disease [25].

CONCLUSION

This review of the literature indicates that ozone therapy holds significant promise in managing periodontitis by exerting antimicrobial effects, reducing inflammation, and modulating oxidative

stress. Studies show that ozone therapy significantly lowers levels of inflammatory biomarkers such as MMP-8, increases the antioxidant capacity of saliva and accelerates the healing of periodontal tissue.

In addition, ozone therapy also showed an effectiveness equivalent to chlorhexidine in reducing periodontal and peri-implant inflammation, with the advantage of minimal side effects. Furthermore, patients with coexisting type 2 diabetes and periodontitis who received ozone therapy experienced a greater reduction in HbA1c levels than those treated with conventional therapy alone.

These results indicate that ozone therapy is not only beneficial for periodontal health but also potentially in the management of inflammation-related systemic diseases.

Despite extensive evidence demonstrating the benefits of ozone therapy in treating periodontitis, more research is still needed with a broader study design and more standardized methodologies to ensure the effectiveness as well as optimal dosage of these therapies. According to existing studies, ozone therapy shows potential as a therapeutic aid for treating periodontitis and related periodontal disorders.

DECLARATIONS

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Ethical approval

None provided.

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors have made substantial academic and intellectual contributions to the study and have reviewed and approved the revised version.

Use of research reporting tool

This review was systematically carried out following the methodological principles outlined by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

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