



Ozone in Dentistry: An Updated Overview of Current Applications and Future Perspectives

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Abstract

Purpose of Review Oxygen-ozone therapy (OOT) is increasingly applied due to its multiple therapeutic effects, but it is still controversial in the medical community. This review provides a comprehensive overview of the recent clinical literature on OOT in dentistry, exploring its efficacy and current issues.

Recent Findings OOT has a wide range of applications in dentistry, including caries management, endodontics, periodontics, and oral surgery. Overall, the results are promising with very limited adverse effects. The formulations used include gaseous ozone, ozonized water, ozonized gel, and ozonization of various products. A large methodologic heterogeneity currently prevents definitive conclusions and meaningful comparisons between different protocols.

Summary Although not conclusive, current evidence suggests that OOT may offer some advantages as an adjunctive or alternative treatment option in certain clinical conditions. Future research should aim to standardize the reporting methodology of OOT protocols in order to make meaningful comparisons and guide the selection of the best protocols for specific treatment endpoints.

Keywords Dentistry · Gaseous ozone · Oxygen-ozone-therapy · Ozonized water · Ozonized oil · Ozone

Introduction

Ozone (O₃) is an inorganic molecule composed of three covalently bonded oxygen atoms, which has a characteristic pungent odor [1].

Although not a radical molecule, ozone is one of the most powerful oxidants known and has been used in medicine since the nineteenth century due to its multiple beneficial effects [2]. In medical oxygen-ozone therapy (OOT) a gaseous mixture is used, in which ozone makes up no more than 5% of the total, with the remainder being oxygen, which acts as a gas carrier [3, 4].

In addition to an oxidation-related broad-spectrum antimicrobial activity, at low medical concentrations ozone

exerts many therapeutic effects through a mild controlled oxidative stress that induces the activation of antioxidant pathways, thus acting as a bioregulator and triggering anti-inflammatory and immunomodulatory responses, and improving the rheological properties of the blood and the general metabolism [5–7].

OOT has been applied with favorable results in many medical fields, such as pain management, infectious and inflammatory diseases, musculoskeletal disorders, dermatology, and even veterinary medicine, through local injections, insufflations, or autohemotherapy [4, 8, 9]. Despite the positive therapeutic effects of ozone and its derivatives that have been reported in many disciplines, OOT is still a controversial topic in the medical community [3, 10]. This may be due to the fact that, unlike other drugs, ozone does not act directly through traditional drug-receptor interactions [5]. Also, OOT has been somewhat limited due to the potential risk of toxicity associated with excessive exposure to gaseous ozone upon inhalation. Possible adverse effects include headache, vomiting, and irritation of the upper respiratory tract, which may cause sore throat, cough, epiphora, rhinitis, and bronchoconstriction [11]. In addition, systemic administration of OOT, such as autohemotherapy,

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is contraindicated in myocardial infarction, hyperthyroidism, acute alcohol intoxication, severe anemia, thrombocytopenia, active bleeding and pregnancy [12]. However, OOT is safe, well tolerated, and free of adverse effects when administered with modern available technology, in accordance with the manufacturer's instructions and current relevant guidelines and recommendations [2, 13].

Current common applications in dental practice include biofilm reduction, preventive and restorative dentistry, periodontology, endodontics, oral pathology and oral surgery, implantology, wound healing, as well as decontamination of manufacts, management of dentin hypersensitivity, pain and temporomandibular disorders (TMD) [6, 10].

OOT is usually implemented as a complementary strategy, often in combination with traditional treatment. However, standard application protocols have not yet been defined [10]. In addition, other potential applications of OOT are increasingly being reported, and the body of evidence and relevant scientific literature has doubled in the last decade.

Therefore, the purpose of this review is to provide a comprehensive overview of the most recent clinical evidence on ozone applications in different areas of dentistry, focusing on the protocols and formulations used, as well as possible related issues or adverse effects.

Materials and Methods

Search Strategy

We performed a literature search on multiple online databases, such as PubMed/MEDLINE, Scopus and Web Of Science, using the following combination of keywords and corresponding mesh terms: "ozone" and "dentistry", "caries", "periodontal", "endodontic" or "root canal", "oral surgery", "oral pathology", "pediatric dentistry" OR "deciduous teeth". Articles published in the last 5 years (i.e. 2019–2024) concerning clinical studies were considered in order to provide a comprehensive and contemporary overview of the field. Multiple reviews on the topic were also analyzed.

Results

The literature search yielded a total of 2167 results, which decreased to 721 after the removal of duplicates, which was performed using the Rayyan software algorithm [14]. Ultimately, 99 clinical studies and 8 preclinical studies were identified related to the topic. An overview of the studies distribution according to the specific field of application in dentistry and the formulation used is reported in Table 1.

As ozone is not stable, it cannot be stored and it is thus generally produced at the moment of use by devices called ozonisers, which convert oxygen into ozone by means of electrical discharges [3]. Half-life of gaseous ozone in still air at 24 °C and zero humidity is approximately 25 h, however, as airflow, temperature, and humidity increase, the ozone half-life decreases to approximately 40 min [15]. Although gaseous ozone has a relatively short half-life, its association with carriers with aqueous or viscous properties retards its reconversion to oxygen [15]. This allows formulations to be obtained with better handling properties, improved stability, and shelf life, while avoiding the risk of toxicity associated with excessive exposure to gaseous ozone [12]. Therefore, gaseous ozone, ozonized water and ozonized oils can be used alone or in combination, depending on the specific clinical application and the expected therapeutic effects [10, 16].

Ozone Applications in Caries Management

Dental caries is a multifactorial disease, and modern caries management includes a variety of restorative, preventive and minimally invasive strategies that work synergistically together [17, 18]. In this context, ozone has found useful applications in both a preventive and a therapeutic approach [19, 20]. The broad-spectrum antimicrobial properties associated with ozone oxidation have been exploited to reduce cariogenic bacterial load and promote biofilm control [21].

One relevant systematic review, despite some limitations, showed overall a promising trend, leading the authors to conclude that ozone therapy can be a useful tool for reducing the bacterial load in deep dentinal carious lesions [22].

In the present review, 4 additional recent clinical studies investigated the antimicrobial effect of OOT [21, 23–25]. Gaseous ozone (120s, flow rate of 1 L/min, 2100 ppm) [21], ozonated olive [24] and sesame oil [25], and ozonized water [23] were found similarly effective in reducing *S. mutans* and *Lactobacillus* spp and improving oral hygiene indices in adolescents and orthodontic patients compared with fluoridated mouthwash, chlorhexidine (CHX), or non-ozonated oils. CHX was found to be slightly more effective in some aspects, but overall it seems that ozone can be used as a satisfactory alternative to CHX.

Ozone has also been applied to prevent the development or progression of caries and to reverse early carious lesions, thanks to its remineralizing potential [7]. Gaseous ozone (concentration not reported) revealed overall effective in promoting the remineralization of initial caries [26] and in preventing the development of new carious lesions in patients at high risk [27, 28], with comparable or slightly better performances than other agents. The combination of ozone with other preventive agents (e.g. hydroxyapatite,

Table 1 Summary of the number of studies according to the field of application in dentistry and formulation used

Caries management (n = 11)	
Effect on cariogenic bacteria	(n=6 - gas: 3, water: 1, oil: 2)
Remineralization	(n=1 - gas)
Prevention of new lesions	(n=2 - gas)
Post-operative pain, tooth vitality	(n=2 - gas)
Systematic review	(n=1)
Endodontics (n=4)	
Irrigation, disinfection	(n=1- water)
Post-operative pain	(n=3- water: 2; ozonized antiseptics:1)
Systematic review	(n=2)
Pediatric dentistry (n=7)	
Caries management	(n=3- gas)
Antimicrobial action, oral hygiene	(n=2- water:1, gel:1)
Endodontic irrigant	(n=1- water)
Endodontic obturation	(n=2- oil)
Pits and fissure sealants (in vitro)	(n=2- gas)
Systematic review	(n=1)
Periodontology (n=39)	
Adjunct to non-surgical treatment	(n=31- gas: 7, water: 13; oil: 8; gas + water: 3)
Adjunct to surgical therapy	(n=1- gas)
Gingivitis	(n=4- gas:1; water: 2, oil:1)
Oral hygiene	(n=3- water)
Meta-analysis	(n=2)
Implantology (n=7)	
Implant surgery	(n=3- water:1; gas + water: 1; saline + oil:1)
Peri-implant mucositis	(n=4- gas:1; water: 1; oil: 2)
Systematic review	(n=2)
Oral surgery (n=18)	
Third molar extraction	
Healing	(n=4 - water:1; oil: 2; water + oil: 1)
Prevention of alveolar osteitis	(n=3- gas:1; water:1; oil:1)
Treatment of alveolar osteitis	(n=1- gas)
Healing of soft tissues surgical wounds	(n=7- gas:1; oil:6)
Osteonecrosis of the jaw (ONJ)	
Prevention	(n=1- gas)
Treatment	(n=2- gas:1; oil:1)
Meta-analysis	(n=1)
Oral pathology (n=6)	
Traumatic ulcers	(n=1- gas)
Non-surgical treatment of ONJ	(n=1- gas injection)
Radiotherapy-induced oral mucositis	(n=1- water)
Ulcerative oral lesions	(n=3- water:2; oil or water:1)
Systematic review	(n=2)
Other applications (n=10)	
Temporo-mandibular disorders (TMD)	(n=3- gas:2; water:1)
Dentin hypersensitivity	(n=2- gas)
Orthodontic pain	(n=1- gas)
Impressions, orthodontic appliances, dentures (in vitro)	(n=2- gas)
Bleaching (ex vivo)	(n=2- ozonized bleaching agent)

fluoride varnish, octenidine) yielded overall the best results [26, 27].

Promising results emerged also when gaseous ozone was applied to deep carious lesions [29] or accidentally exposed pulp [30] and followed by restoration, with evidence of less

pain and lower occurrence of root canal treatment at follow up, compared to traditional treatment. Overall, no adverse effects were reported. Interestingly, in one study using gaseous ozone, remarkable whitening of ozone-treated teeth was also observed [28].

Ozone Application in Endodontics

Among the factors influencing the success of endodontic treatment, the effectiveness of chemo-mechanical disinfection procedures plays a key role [31]. It is also important that the chemical irrigants and the obturation materials used are not cytotoxic to the periodontal environment in the event of accidental periapical extrusion [32]. Because of its antimicrobial and biostimulatory properties and proven biocompatibility, ozone therapy has thus been studied as an adjunctive strategy in endodontics.

In agreement with recent reviews [31, 33], overall, ozonized water and ozonized antiseptic solutions did not perform better as compared to other traditional irrigants such as sodium hypochlorite (NaOCl) and CHX in terms of antibacterial activity, thus it is not generally indicated neither to replace nor to complement these agents. However, in some cases ozone reached comparable antibacterial activity, highlighting that its effect was strongly associated with the protocol used, in a dose, time and bacterial strain-dependent way, thereby representing a possible alternative in selected cases [34].

On the other hand, ozonized water and ozonized antiseptics showed promising results in terms of reduction of postoperative pain after endodontic treatment or retreatment procedures [35–37]. The concentration of ozone in water was however reported only in one study (1.86 µg/ml) [35].

Ozone Applications in Pediatric Dentistry

Because of its antibacterial and remineralizing properties, ozone has been implemented also in the management of caries and endodontic treatment of primary teeth [38].

With regards to application for treatment of caries in primary dentition, a recent review considering also the studies retrieved in this review [39–42] concluded that, despite some limitations and a great methodological heterogeneity, ozone seems comparable to other interventions in terms of clinical outcomes and reduction of bacterial count, regardless of the protocol applied, with no reported adverse effects and good patient acceptance [38]. Therefore, ozone application may be a non-invasive approach to treat caries in primary dentition, especially in very young and poorly cooperative patients. Also, an effective reduction of plaque index, *S. mutans* count and consequent improvement of oral health status in children was obtained with ozonized water (2 ppm) rinses and ozonized oil (20 ppm), with results comparable to CHX formulations [43, 44].

In endodontic applications, ozonized water was found to be an effective irrigant in reducing anaerobic bacteria in root canals of primary teeth compared to saline and herbal tea [45]. When used in addition to zinc-oxide-eugenol (ZOE)

cement as an obturating material in pulpectomy of primary teeth, ozonized oil showed promising results, with better clinical and radiographic outcomes at follow-up compared to ZOE alone [32, 46].

The application of gaseous ozone (40s application at 60–80 µg/mL) before placement of pits and fissure sealants *ex vivo*, especially when used after acid etching, resulted in significantly less microleakage and better penetration than traditional sealant application, with no effects on the bond strength [47]. On the other hand, a 30s application at 100 µg/mL before etching yielded no significant differences in the etching pattern and surface area obtained but resulted in lower surface roughness values as compared to 5.25% NaOCl, suggesting a better performance for NaOCl [48].

Finally, ozone has been indicated as an important tool in the management of severe cases of molar-incisor hypomineralization (MIH), allowing the reversal of dentin hypersensitivity, improving remineralization and promoting the maintenance of tooth vitality by decontaminating enamel or dentin layers before the placement of bioactive sealants or restorations [49].

Ozone Applications in Periodontology

Because ozone has demonstrated antimicrobial properties, including against anaerobic bacteria involved in the pathogenesis of periodontitis, and promotes anti-inflammatory and regenerative biological processes, many studies have been conducted to evaluate its efficacy as an adjunctive tool in the management of periodontal disease.

The most commonly studied outcomes are clinical parameters, such as bleeding scores, clinical attachment loss, plaque index, gingival index, microbiological parameters, including qualitative and quantitative characterization of anaerobic periodontopathogens, and quantification of inflammatory biomarkers, including interleukins, oxidant and antioxidant status, and gingival crevicular fluid (GCF). Two recent meta-analyses including randomized clinical trials (RCTs) published up to 2019 reported controversial conclusions: despite the methodological heterogeneity, there is an overall indication of ozone therapy being effective as an adjunct to scaling and root planing (SRP) in the treatment of periodontitis, although the differences were not statistically significant as compared to CHX application or SRP alone [50, 51].

The studies identified in the present review overall confirmed this trend: regardless of the protocol applied, OOT applications in non-surgical management of periodontitis or gingivitis showed overall results comparable to photodynamic therapy (PDT), photobiomodulation therapy (PBMT) or CHX [52], mostly superior to traditional treatment without ozone, in terms of clinical and microbiological

parameters, as well as biomarkers of inflammation. However, when gaseous ozone was used in adjunct to surgical regenerative periodontal treatment, no significant beneficial effects emerged [53].

Ozonized water rinses have proven to be useful in special needs patients improving clinical and microbiological parameters, and overall oral health status, without adverse effects [54, 55]. However, the authors highlighted that a recent review reported that certain antiseptic mouthwashes, not CHX specifically, may be responsible for the increased risk of mortality through interference with the nitric oxide pathway. Therefore, the safety of ozonated mouthwashes needs to be confirmed in larger series before they can be considered as an alternative to CHX in oral care [54].

Conversely, Nicolini et al. reported no beneficial effects on oral hygiene parameters for ozonized water (bubbled at 70 µg/ml for 10 min) compared to double-distilled water mouthrinses, along with the occurrence, albeit in a small number of subjects, of transient mild adverse effects such as burning sensation and taste discomfort that resolved spontaneously within 24 h [56].

Periodontal patients with type 2 diabetes mellitus were found to have beneficial, although not statistically significant, improvements in glycated hemoglobin (HbA1C), inflammatory biomarkers, and clinical parameters using a combined protocol of gaseous ozone and ozonated water rinses and mouthwashes in adjunct to SRP [57, 58].

Ozone Applications in Implant Surgery

In terms of healing in the post-operative period following implant placement, regardless of the formulations and protocols used, all of the studies reported positive effects with less pain and inflammation, as well as improved early healing [59–61]. Similarly, ozone provided a significant advantage in improving disease-related radiographic defects and gene expressions, as well as clinical parameters of peri-implant mucositis [62]. These findings were also confirmed by recent relevant systematic reviews [63, 64]. Gaseous ozone, ozonized water (0.05 to 25 µg/mL) and oil were used equally.

Ozone Applications in Oral Surgery

Thanks to its biostimulating and decontaminating properties, ozone applications have been studied in the fields of extractive surgery, management of complications following extractions, such as osteonecrosis of the jaw (ONJ) and alveolar osteitis (dry socket), and in the surgery of oral soft tissues, such as palatal grafts, gingival surgery and removal of pigmentation by laser surgery [65, 66]. Overall, regardless of the formulation applied, ozone therapy showed

beneficial effects in all fields, as compared to controls, and was associated with lower incidence of post-surgical complications, lower pain scores and faster healing. In particular, the association of gaseous ozone and concentrated growth factors yielded the best outcomes in the treatment of dry socket [67]. These findings were further confirmed by a meta-analysis that investigated the efficacy of adjuvant ozone therapy in the management of post-surgical complications following impacted mandibular third-molar surgery [68]. Interestingly, one RCT reported that ozonated oil was as effective as conventional analgesics and antibiotics in the post-operative management of pain and inflammation, suggesting that it may be a safe and effective alternative [69]. Conversely, in one study, the use of ozonated oil resulted in worse surgical wound healing outcomes compared to platelet rich fibrin (PRF) [70], and in two studies, it did not improve healing and even caused an increase in oxidative stress and decreased quality of life in patients; the authors reported that this may have been due to the high dose and overapplication [71, 72].

Ozone Applications in Oral Pathology

Ozone applications have been studied as an adjunct or alternative treatment for erosive or ulcerative oral lesions of different etiology, such as erosive oral lichen planus, cancer-therapy induced oral mucositis, traumatic ulcers and infectious diseases [73–77]. Overall, promising results emerged from the clinical studies identified in the present review, with faster healing times, lower pain scores and lower incidence and severity of oral mucositis. In particular, one study reported better outcomes using ozonized oil if compared to ozonized water irrigations [73]. These findings are also supported by two recent systematic reviews, which concluded that despite the lack of standardized protocols, ozone therapy appears to be beneficial in providing shorter healing times, reduced pain and lesion severity, and no adverse effects, thus representing a safe and reliable alternative treatment for patients suffering from soft tissue lesions [78, 79].

Other Applications

Ozone therapy has found potential uses in a number of other diverse areas. For example, ozone applications as an irrigant during arthrocentesis (20 µg/mL) or as a transdermal gas application (10–100 µg/mL) have been successful in managing TMD-related pain and improving mandibular function [80–82]. Though not superior to occlusal splint, OOT can be considered as non-invasive, faster, and more comfortable treatment alternative [80, 83]. Gaseous ozone (32 g/m³) was also effective in the treatment of dentin

hypersensitivity, with better results compared to diode laser [84] and application of a bonding agent [85]. Conversely, no beneficial effects of gaseous ozone applications were reported in a study regarding the management of pain associated with orthodontic therapy [86].

The disinfectant action of ozone was found to be useful for the decontamination of clear aligners [87], with results comparable to CHX, suggesting its possible use as part of the manufacturing process, as well as for elastomeric impressions, equaling or outperforming other disinfectant solutions, without altering material properties [88, 89].

Regarding the bleaching properties of ozone, two recent *ex vivo* studies reported promising results: 10% ozonized (60 µg/mL) carbamide peroxide (CP) was as effective as CP alone in terms of whitening, but with a significantly shorter application time, less enamel surface modification, and a more stable pH [90, 91].

Finally, intraperitoneal insufflation of gaseous ozone showed promising potential for nerve regeneration in rats with facial nerve injury, with better healing outcomes compared to low-level laser therapy (LLLT) and control groups [92].

Discussion

Ozone therapy has many diverse applications in dentistry and is being investigated by a growing body of evidence. Although sometimes not supported by statistical significance, authors generally report an indication of clinically relevant efficacy [51, 58, 65, 66, 93].

As a side note, this also raises the important issue of the traditionally accepted (and often required) dichotomous approach of statistical significance as a definitive interpretation of findings, which may not necessarily reflect actual relevant clinical differences [94]. In light of this, a thoughtful reconsideration of this trend in all scientific fields should be encouraged, as already recommended by relevant methodological literature and scientific societies [95–97].

In some studies where no beneficial effects were found for ozone as an adjunct therapy compared to controls [53, 86, 98], or where the results were generally positive but the differences were not statistically significant [57, 58, 99, 100] open system ozone generators were used, which typically produce low concentrations of ozone and do not allow accurate dose measurement [6]. These devices produce ozone from the oxygen naturally present in the ambient air through a glass handpiece and are reported to achieve ozone concentrations of 10 to 100 µg/mL. This varies according to the different programs used, is not consistent from one device to another, and furthermore, a concentration of 100 µg/ml appears difficult to reach using ambient oxygen as the

feed [6, 11, 22]. Conversely, other types of devices produce ozone from pure medical oxygen drawn from a cylinder and are able to achieve higher concentrations and precise monitoring through built-in spectrophotometers [84].

Some authors reported using very low concentrations in ozonized water (e.g. 0.01 mg/L) [101] or oil [25], so the minimal difference found compared to the respective control products without ozone is somewhat to be expected.

It is interesting to note that according to some studies on antimicrobial activity, ozone seems to be generally more effective against *S. mutans* and less effective against *Lactobacilli*, regardless of the formulation used [21, 23]. Similar findings have been reported in endodontic studies, suggesting that ozone's disinfectant activity is also strain dependent to some extent [31, 34].

With regards to pediatric dentistry, it is worth noting that ozone derivatives with small or even comparable beneficial effects to other traditional antiseptics, such as CHX and NaOCl, may offer some advantages in terms of safety and compliance. In fact, the use of ozonized water as a mouthwash may prevent decreased compliance in children due to the taste of CHX [17, 45]. Ozonized water may be safer as an endodontic irrigant and, like ozonized oil, may provide an additional disinfectant effect when added to root canal obturation material in primary teeth [32, 46].

In some cases, high concentrations of ozone, worsened the oxidative status and did not improve healing [70–72]. Similar to other studies, where moderate concentrations yielded the best results, this confirms the typical hormetic model of ozone therapeutic effects [3, 5].

A common issue of most literature on the topic is the great heterogeneity of protocols applied, in terms of ozone formulations, time and method of application, and outcomes considered. This prevents meaningful comparisons between the studies, as reported in recent systematic reviews on specific dental applications, where meta-analysis could not be performed [22, 31, 38, 63, 64, 78, 102].

Concentration information is often inaccurate, confusing, or not reported at all [103, 104].

The concentration of ozone has been reported using a variety of units of measurement in different studies that employed the same formulations (g/m³, ppm, mg/L, µg/mL, etc.) It should be noted that the concentration of gaseous ozone can be considered in oxygen or in air and, although using ppm is correct, it is typically measured in units of mass of ozone (i.e., µg or mg or g) per volume of air/oxygen (i.e., cm³, dm³, m³ equivalent to mL, L, 1,000 L, respectively) and is generally based on the principles of wet chemistry [105]. On the other hand, parts per million (ppm) can also be expressed as milligrams of ozone per liter of solvent (mg/L) when ozone is solubilized in a liquid. This indicates

the mass of a chemical or contaminant per unit volume of water [105].

Furthermore, it is sometimes unclear whether the ozone concentration reported refers to the initial gaseous ozone concentration or the amount of ozone actually present in the final derivative product [66, 74]. This is especially true with ozonized oil. Because ozone does not dissolve in oil, but rather reacts chemically with the double bonds of the fatty acids, it forms specific ozonides and peroxides that actually “contain” the oxidizing power of the ozonized oil [106]. Therefore, in addition to the concentration of ozone gas used (typically up to 70 µg/ml), the authors should also provide specific information on the type and amount of oil used, the reaction time and the temperature at which the process was performed, which are aspects of major interest that directly influence the therapeutic activity of these functional products [6, 107].

Another important issue that needs to be highlighted is the general lack of information on the amount of peroxide species in these products (i.e. the actual peroxide value), possibly due to the lack of a standard method to express it, which ultimately prevents comparison between different ozone derivatives [106].

Also, it is worth mentioning that ozonized oils are often inappropriately referred to as gels, leading to terminological confusion: the increase in viscosity that occurs naturally as a result of ozonization does not justify the use of the term gel for the derivative obtained [106]. Therefore, it is recommended that clinicians approaching ozone therapy have an adequate knowledge of the basic principles of ozone physics and chemistry. On the other hand, manufacturers should be encouraged to provide detailed information on ozone devices and derivatives.

Finally, since the effects of OOT are related to the action of reactive oxygen species (ROS) and lipid oxidation products (LOPs) produced after ozone interaction with blood, tissue or serum, clinicians must consider that the amount of these functional by-products also varies depending on the form of ozone administration, so that specific pathological conditions will require specific treatment protocols [5, 6, 11]. Unfortunately, there is an almost complete lack of studies comparing different ozone protocols, which would provide useful information to guide protocol selection for specific diseases.

Despite the limitations inherent in the narrative design of the present review and the absence of quantitative analyses, this review provides a valuable and comprehensive overview of the most recent state of the art in OOT in dentistry and outlines future research perspectives as well as current research gaps.

Conclusions

Ozone therapy has been used for a variety of applications in dentistry and it appears that the overall results are promising, with no or very limited adverse effects reported in all areas and formulations used. This paves the way for further applications. However, great heterogeneity in study protocols and a lack of standardized methods for reporting the functional characteristics of ozone treatment have emerged.

As a result, conclusive analyses and comparisons between studies are generally not possible, and the additional paucity of studies comparing different protocols makes it difficult to identify the best dosage and route of administration. These are important issues that need to be urgently addressed by future research in this field. Ultimately, this will help to identify specific and effective protocols for different clinical applications of OOT.

Key References

- El-Desouky SS, Omer SMM, Ghouraba RF, Latif R, Kabbash IA, Hadwa SM. Zinc oxide-ozonated olive oil as a new root canal filling material in primary molars: a clinical randomized controlled trial. *Clin Oral Investig*. 2023;27:7395–405. <https://doi.org/10.1007/s00784-023-05329-z>.

An interesting clinical study on the potential use of ozonized products as intracanal obturation for primary teeth.

- Franzini M, Tirelli U, Valdenassi L, Vaiano F, Galoforo AC, Ricevuti G, Chirumbolo S. Oxygen-ozone therapy in the medical sciences. State of art. *Int Immunopharmacol*. 2024;137:112489. <https://doi.org/10.1016/j.intimp.2024.112489>.

This paper provides a comprehensive insight of the therapeutical mechanisms and uses of oxygen-ozone therapy.

- Shetty N, Mathew T, Shetty A, Hegde MN, Attavar S. Ozonated water as an irrigant in disinfecting root canal systems - a systematic review. *Evid Based Dent*. 2022. <https://doi.org/10.1038/s41432-022-0800-7>.

An interesting review on the use and effectiveness of ozonized products for disinfection of root canals.

- Torres-Rosas R, Marcela Castro-Gutiérrez ME, Flores-Mejía LA, Torres-Rosas EU, Nieto-García RM,

Argueta-Figueroa L. Ozone for the treatment of temporomandibular joint disorders: A systematic review and meta-analysis. *Med Gas Res.* 2023;13:149–54. <https://doi.org/10.4103/2045-9912.345174>.

A comprehensive overview on ozone applications in temporomandibular disorders.

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Declarations

Human and Animal Rights and Informed Consent No animals or humans were used in this study.

Competing Interests The authors declare no competing interests.

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References

- Swanson TJ, Jamal Z, Chapman J. Ozone toxicity. StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.
- Lynch E. Ozone: the revolution in dentistry. Copenhagen: Quintessence; 2004.
- Bocci V, Borrelli E, Travagli V, Zanardi I. The ozone paradox: ozone is a strong oxidant as well as a medical drug. *Med Res Rev.* 2009;29:646–82. <https://doi.org/10.1002/med.20150>.
- Franzini M, Tirelli U, Valdenassi L, Vaiano F, Galoforo AC, Ricevuti G, Chirumbolo S. Oxygen-ozone therapy in the medical sciences. State of art. *Int Immunopharmacol.* 2024;137:112489. <https://doi.org/10.1016/j.intimp.2024.112489>.
- Bocci VA, Zanardi I, Travagli V. Ozone acting on human blood yields a hormetic dose-response relationship. *J Transl Med.* 2011;9:66. <https://doi.org/10.1186/1479-5876-9-66>.
- Tricarico G, Rodrigues Orlandin J, Rocchetti V, Ambrosio CE, Travagli V. A critical evaluation of the use of ozone and its derivatives in dentistry. *Eur Rev Med Pharmacol Sci.* 2020;24:9071–93. https://doi.org/10.26355/eurrev_202009_22854.
- Veneri F, Filippini T, Consolo U, Vinceti M, Generali L. Ozone therapy in dentistry: an overview of the biological mechanisms involved (review). *Biomed Rep.* 2024;21:115. <https://doi.org/10.3892/br.2024.1803>.
- De Sire A, Marotta N, Ferrillo M, Agostini F, Sconza C, Lippi L, Respizzi S, Giudice A, Invernizzi M, Ammendolia A. Oxygen-ozone therapy for reducing pro-inflammatory cytokines serum levels in Musculoskeletal and Temporomandibular disorders: a Comprehensive Review. *Int J Mol Sci.* 2022;23:2528. <https://doi.org/10.3390/ijms23052528>.
- Hidalgo-Tallón FJ, Torres-Morera LM, Baeza-Noci J, Carrillo-Izquierdo MD, Pinto-Bonilla R. Updated review on ozone therapy in Pain Medicine. *Front Physiol.* 2022;13:840623. <https://doi.org/10.3389/fphys.2022.840623>.
- Barczyk I, Maslyk D, Walczuk N, Kijak K, Skomro P, Gronwald H, Pawlak M, Rusińska A, Sadowska N, Gronwald B, Garstka AA, Lietz-Kijak D. Potential clinical applications of ozone therapy in dental specialties—a literature review, supported by own observations. *Int J Environ Res Public Health* 2023;20. <https://doi.org/10.3390/ijerph20032048>.
- D'Amario M, Di Carlo M, Natale SM, Memè L, Marzo G, Matarazzo G, Capogreco M. Application of ozone therapy in Paediatric Dentistry. *Appl Sci.* 2022;12:11100. <https://doi.org/10.3390/app122111100>.
- Gupta S, Deepa D. Applications of ozone therapy in dentistry. *J Oral Res Rev.* 2016;8:86–91. <https://doi.org/10.4103/2249-4987.192243>.
- International Scientific Committee of Ozone Therapy–ISCO3. Learning methodology instructions and perfection in ozone therapy for medical doctors. 2015. <https://isco3.org/wp-content/uploads/2015/09/ISCO3-HUM-00-01.pdf>
- Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev.* 2016;5:210. <https://doi.org/10.1186/s13643-016-0384-4>.
- Viebahn-Haensler R, León Fernández OS. Ozone in Medicine. The low-dose ozone Concept and its basic biochemical mechanisms of Action in Chronic Inflammatory diseases. *Int J Mol Sci.* 2021;22:7890. <https://doi.org/10.3390/ijms22157890>.
- Smith NL, Wilson AL, Gandhi J, Vatsia S, Khan SA. Ozone therapy: an overview of pharmacodynamics, current research, and clinical utility. *Med Gas Res.* 2017;7:212–9. <https://doi.org/10.4103/2045-9912.215752>.
- Cardoso M, Coelho A, Lima R, Amaro I, Paula A, Marto CM, Sousa J, Spagnuolo G, Marques Ferreira M, Carrilho E. Efficacy and patient's Acceptance of Alternative methods for caries Removal—A systematic review. *J Clin Med.* 2020;9:3407. <https://doi.org/10.3390/jcm9113407>.
- Veneri F. Fluoride and caries prevention: a scoping review of public health policies. *Annali Di Igiene Med Preventiva E Di Comunità.* 2024;36:270–80. <https://doi.org/10.7416/ai.2024.2593>.
- AlMogbel AA, Albarrak MI, AlNumair SF. Ozone therapy in the Management and Prevention of Caries. *Cureus.* 2023. <https://doi.org/10.7759/cureus.37510>.
- Santos GM, Pacheco RL, Bussadori SK, Santos EM, Riera R, De Oliveira Cruz Latorraca C, Mota P, Benavent Caldas Bellotto EF, Martimbianco ALC. Effectiveness and safety of ozone therapy in Dental Caries Treatment: systematic review and Meta-analysis. *J Evid Based Dent Pract.* 2020;20:101472. <https://doi.org/10.1016/j.jebdp.2020.101472>.
- Düzyol E, Gürbüz T, Baris Ö. Antimicrobial efficacy of ozone therapy on cariogenic bacteria. *Meandros Med Dent J.* 2021;22:1–7. <https://doi.org/10.4274/MEANDROS.GALENOS.2020.18853>.
- Badhe H, Kalaskar R, Balasubramanian S, Kamki H, Kalaskar A. Antimicrobial effect of ozone therapy in Deep Dental Carious

- Lesion: a systematic review. *Int J Clin Pediatr Dent.* 2022;15:S252–60. <https://doi.org/10.5005/jp-journals-10005-2168>.
23. Madhu PP, Prashant GM, Kumar PGN, Sushanth VH, Imranulla M, Vivek H. Comparative evaluation of cranberry extract mouth rinse, ozonized water and 0.2% chlorhexidine on salivary *Streptococcus mutans* and *lactobacilli* count: an in-vivo study. *Int J Ayurvedic Med.* 2023;14:268–73.
 24. Shahi AK, Kumar P, Shetty D, Jain A, Sharma P, Raza M. Effect of antimicrobial agents on the oral microflora in patients undergoing fixed orthodontic therapy-An ex vivo comparative analysis. *J Orthod Sci.* 2021;10:12. https://doi.org/10.4103/jos.JOS_46_20.
 25. Vadhana VC, Sharath A, Geethapriya PR, Vijayasankari V. Effect of sesame oil, ozonated sesame oil, and chlorhexidine mouthwash on oral health status of adolescents: a randomized controlled pilot trial. *J Indian Soc Pedod Prev Dent.* 2019;37:365–71. https://doi.org/10.4103/jisppd.Jisppd_244_19.
 26. Grocholewicz K, Matkowska-Cichocka G, Makowiecki P, Drożdżik A, Ey-Chmielewska H, Dziewulska A, Tomasik M, Trybek G, Janiszewska-Olszowska J. Effect of nano-hydroxyapatite and ozone on approximal initial caries: a randomized clinical trial. *Sci Rep.* 2020;10:11192. <https://doi.org/10.1038/s41598-020-67885-8>.
 27. Grocholewicz K, Mikłasz P, Zawisłak A, Sobolewska E, Janiszewska-Olszowska J. Fluoride varnish, ozone and octenidine reduce the incidence of white spot lesions and caries during orthodontic treatment: randomized controlled trial. *Sci Rep.* 2022;12:13985. <https://doi.org/10.1038/s41598-022-18107-w>.
 28. Kirilova J, Kirov D. Prevention of dental caries in caries-active individuals by gaseous ozone. *J IMAB.* 2023;29:4805–9. <https://doi.org/10.5272/jimab.2023291.4805>.
 29. AL-Omiri MK, Alqahtani NM, Alahmari NM, Hassan RA, Al Nazeah AA, Lynch E. Treatment of symptomatic, deep, almost cariously exposed lesions using ozone. *Sci Rep.* 2021;11:11166. <https://doi.org/10.1038/s41598-021-90824-0>.
 30. Dikopova NZH, Volkov AG, Kopecki IS, Nikolskaya IA, Margaryan EG, Budina TV, Samokhlib YAV, Kondratiev SA, Paramonov YUO, Arakelyan MG. Clinical and experimental validation of the ozone therapy effectiveness in case of accidental exposure of the dental pulp. *New Armen Med J.* 2021;15:77–84.
 31. Silva EJNL, Prado MC, Soares DN, Hecksher F, Martins JNR, Fidalgo TKS. The effect of ozone therapy in root canal disinfection: a systematic review. *Int Endod J.* 2020;53:317–32. <https://doi.org/10.1111/iej.13229>.
 32. Vachhani K, Rao D, Panwar S, Gupta S. An in vivo comparative clinical and radiographic evaluation of a mixture of zinc oxide-Ocimum sanctum extract, zinc oxide-ozonated oil, and zinc oxide-eugenol as obturating materials in primary molars. *J Indian Soc Pedod Prev Dent.* 2022;40:398–403. https://doi.org/10.4103/jisppd.jisppd_204_22.
 33. Shetty N, Mathew T, Shetty A, Hegde MN, Attavar S. Ozonated water as an irrigant in disinfecting root canal systems - a systematic review. *Evid Based Dent.* 2022. <https://doi.org/10.1038/s41432-022-0800-7>.
 34. Mehta N, Gupta A, Mahesh S, Abraham D, Singh A, Jala S, Chauhan N, Sreen D. Comparative evaluation of antibacterial efficacy of Allium sativum extract, aqueous ozone, diode laser, and 3% sodium hypochlorite in root canal disinfection: an in vivo study. *J Conserv Dent.* 2020;23:577–82. https://doi.org/10.4103/jcd.Jcd_405_20.
 35. Sağlam H, Aladağ H. Comparison of intracanal ozone and low-level laser therapy on postoperative pain in vital teeth with symptomatic apical periodontitis: placebo-controlled randomized trial. *Lasers Med Sci.* 2023;38:227. <https://doi.org/10.1007/s10103-023-03881-4>.
 36. Sinha N, Asthana G, Parmar G, Langaliya A, Shah J, Singh B. Evaluation of postoperative pain in endodontic retreatment with apical periodontitis using ozonated 2% chlorhexidine and 0.1% octenidine application: a randomized clinical trial. *J Conserv Dent Endod.* 2024;27:654–61. https://doi.org/10.4103/jcde.Jcde_146_24.
 37. Sinha N, Asthana G, Parmar G, Langaliya A, Shah J, Kumbhar A, Singh B. Evaluation of ozone therapy in Endodontic Treatment of Teeth with necrotic pulp and apical periodontitis: a Randomized Clinical Trial. *J Endod.* 2021;47:1820–8. <https://doi.org/10.1016/j.joen.2021.09.006>.
 38. Veneri F, Filippini T, Consolo U, Vinceti M, Generali L. Ozone treatment for the management of Caries in primary dentition: a systematic review of Clinical studies. *Dentistry J.* 2024;12:69. <https://doi.org/10.3390/dj12030069>.
 39. Alhashmi AA, Mohammed RAK, Hasan MS. An innovative technique for treating severe caries in primary teeth with ozone: a retrospective investigation. *J Pharm Negat Results.* 2023;14.
 40. Beretta M, Federici Canova F. A new method for deep caries treatment in primary teeth using ozone: a retrospective study. *Eur J Paediatr Dent.* 2017;18:111–5. <https://doi.org/10.23804/ejpd.2017.18.02.05>.
 41. Luppieri V, Manfra A, Ronfani L, Chermetz M, Cadenaro M. Ozone Therapy for Early Childhood Caries (ECC) treatment: an in vivo prospective study. *Appl Sci.* 2022;12:1964. <https://doi.org/10.3390/app12041964>.
 42. Mese M, Tok YT, Kaya S, Akcay M. Influence of ozone application in the stepwise excavation of primary molars: a randomized clinical trial. *Clin Oral Invest.* 2020;24:3529–38. <https://doi.org/10.1007/s00784-020-03223-6>.
 43. Adhami ZE, Erfanparast L, Molaei Z, Sadeghi J, Yazdanparast A. Effect of 20-ppm ozone and 1% chlorhexidine gels on plaque index and *Streptococcus mutans* counts in the dental plaque in 6-12-year-old children: a randomized, double-blind clinical trial. *J Dent Res Dent Clin Dent Prospects.* 2023;17:177–81. <https://doi.org/10.34172/joddd.2023.40461>.
 44. Mon J, Asokan S, Priya PR, Kumar TD, Balasubramaniam MG. Effect of Herbal Water, Ozonated Water, Water, and Chlorhexidine Mouthrinses on oral health status of children: a Randomized Controlled Trial. *Int J Clin Pediatr Dent.* 2019;12:514–9. <https://doi.org/10.5005/jp-journals-10005-1693>.
 45. Agarwal S, Tyagi P, Deshpande A, Yadav S, Jain V, Rana KS. Comparison of antimicrobial efficacy of aqueous ozone, green tea, and normal saline as irrigants in pulpectomy procedures of primary teeth. *J Indian Soc Pedod Prev Dent.* 2020;38:164–70. https://doi.org/10.4103/JISPPD.JISPPD_119_20.
 46. El-Desouky SS, Omer SMM, Ghouraba RF, Latif R, Kabbash IA, Hadwa SM. Zinc oxide-ozonated olive oil as a new root canal filling material in primary molars: a clinical randomized controlled trial. *Clin Oral Investig.* 2023;27:7395–405. <https://doi.org/10.1007/s00784-023-05329-z>.
 47. Bezgin T, Oz FT, Ozalp N. Efficacy of ozone pretreatment on Fissure Sealant Adaptation and Retention. *OZONE-SCIENCE Eng.* 2022;44:317–23. <https://doi.org/10.1080/01919512.2021.1919054>.
 48. Gandhi M, Lakade L, Davalbhakta R, Patel A, Chaudhary S, Jajoo S. Scanning electron microscope analysis to evaluate the effect of pretreatment with ozone and sodium hypochlorite on pits and fissures of primary teeth. *J Indian Soc Pedod Prev Dent.* 2023;41:258–64. https://doi.org/10.4103/jisppd.jisppd_352_23.
 49. Beretta M, Canova FF, Moscati M, Campanella V, Gallusi G. State-of-the-art on MIH. Part. 2 MIH clinical management using ozone. *Eur J Paediatr Dent.* 2020;21:163–6. <https://doi.org/10.23804/ejpd.2020.21.02.13>.
 50. Deepthi R, Bilichodmath S. Ozone therapy in Periodontics: a Meta-analysis. *Contemp Clin Dent.* 2020;11:108–15. https://doi.org/10.4103/ccd.ccd_79_19.
 51. Moraschini V, Kischinhevsky ICC, Calasans-Maia MD, Shibli JA, Sartoretto SC, Figueredo CM, Granjeiro JM. Ineffectiveness of ozone therapy in nonsurgical periodontal treatment: a

- systematic review and metaanalysis of randomized clinical trials. *Clin Oral Investig.* 2020;24:1877–88. <https://doi.org/10.1007/s00784-020-03289-2>.
52. Talasani RR, Potharaju SP, Vijaya Lakshmi B, Durga Bai Y, Chintala RK, Mahankali V, Koppolu P, AlGhamdi ARS. Efficacy of ozonated water over chlorhexidine mouth rinse in chronic gingivitis patients - a comparative clinical study. *Saudi Dent J.* 2022;34:738–43. <https://doi.org/10.1016/j.sdentj.2022.09.004>.
 53. Cetiner DO, Isler SC, Ilikci-Sagkan R, Sengul J, Kaymaz O, Corekci AU. The adjunctive use of antimicrobial photodynamic therapy, light-emitting-diode photobiomodulation and ozone therapy in regenerative treatment of stage III/IV grade C periodontitis: a randomized controlled clinical trial. *Clin Oral Investig.* 2024;28:426. <https://doi.org/10.1007/s00784-024-05794-0>.
 54. Izadi M, Bagheri M, Far AB, Sureda A, Soodmand M. Effect of ozonated water and chlorhexidine mouthwash on oral health in critically ill patients on mechanical ventilation: a double-blind randomised clinical trial. *Intensive Crit Care Nurs* 2021;66. <https://doi.org/10.1016/j.iccn.2021.103083>.
 55. Tatuskar PV, Karmakar S, Walavalkar NN, Vandana KL. Effect of ozone irrigation and powered toothbrushing on dental plaque, gingival inflammation, and microbial status in institutionalized mentally challenged individuals: a double-blinded, randomized, controlled clinical trial. *J Indian Soc Periodontol.* 2023;27:315–9. https://doi.org/10.4103/jisp.jisp_69_22.
 56. Nicolini AC, Rotta IDS, Langa GPJ, Friedrich SA, Arroyo-Bonilla DA, Wagner MC, Weidlich P, Rösing CK, Cavagni J. Efficacy of ozonated water mouthwash on early plaque formation and gingival inflammation: a randomized controlled crossover clinical trial. *Clin Oral Investig.* 2021;25:1337–44. <https://doi.org/10.1007/s00784-020-03441-y>.
 57. Rapone B, Ferrara E, Qorri E, Inchingolo F, Isola G, Dongiovanni P, Tartaglia GM, Scarano A. Research efficacy of gaseous ozone therapy as an adjuvant to periodontal treatment on oxidative stress mediators in patients with type 2 diabetes: a randomized clinical trial. *BMC Oral Health.* 2023;23:278. <https://doi.org/10.1186/s12903-023-02985-1>.
 58. Rapone B, Ferrara E, Corsalini M, Converti I, Grassi FR, Santacroce L, Topi S, Gnoni A, Scacco S, Scarano A, Delvecchio M. The effect of gaseous ozone therapy in conjunction with periodontal treatment on glycated hemoglobin level in subjects with type 2 diabetes mellitus: an unmasked Randomized Controlled Trial. *Int J Environ Res Public Health* 2020;17. <https://doi.org/10.3390/ijerph17155467>.
 59. Dixit A, Agarwal B, Singh K, Chand P, Rao J, Mishra N. Comparative evaluation of normal saline gel and ozone therapy on soft and hard tissue health in Dental Implant surgery. *Indian J Dent Res.* 2024;35:2–6. https://doi.org/10.4103/ijdr.ijdr_591_23.
 60. Sghaireen MG, Alzarea BK, Alduraywish AA, Alam MK, Srivastava KC, Khader Y, Dar-Odeh N, Ganji KK. Effect of aqueous ozone solution irrigation on Healing after Treatment with Dental implants: a cross-over Randomized Controlled Clinical Trial. *J Hard Tissue Biol.* 2020;29:263–6.
 61. Shekhar A, Srivastava S, Kumar Bhati L, Chaturvedi A, Singh S, Agarwal B, Arora K. An evaluation of the effect of ozone therapy on tissues surrounding dental implants. *Int Immunopharmacol.* 2021;96:107588. <https://doi.org/10.1016/j.intimp.2021.107588>.
 62. Isler SC, Soysal F, Akca G, Bakirarar B, Ozcan G, Unsal B. The effects of decontamination methods of dental implant surface on cytokine expression analysis in the reconstructive surgical treatment of peri-implantitis. *Odontology.* 2021;109:103–13. <https://doi.org/10.1007/s10266-020-00520-0>.
 63. Randi CJ, Heiderich CMC, Serrano RV, Morimoto S, de Moraes LOC, Campos L, Palma LF. Use of ozone therapy in Implant Dentistry: a systematic review. *Oral Maxillofac Surg.* 2023. <https://doi.org/10.1007/s10006-023-01149-3>.
 64. Shah B, Rajasekar A. Clinical efficacy of ozone therapy in Peri-implant diseases: a systematic review. *J Clin Diagn Res.* 2024;18:ZC31–6. <https://doi.org/10.7860/JCDR/2024/71032.19642>.
 65. Ahmedi J, Agani Z, Abdyli RA, Loxha MP, Hamiti-Krasniqi V, Rexhepi A, Stubljarić D. Comparison between ozone and CHX gel application for reduction of pain and incidence of dry socket after lower third molar removal. *Clin Exp Dent Res.* 2023;9:75–81. <https://doi.org/10.1002/cre2.675>.
 66. Patil SS, Patil SM, Rakhewar P, Chacko L, Lihe V, Kulkarni K. Comparison of effect of ozone oil and non-eugenol periodontal dressing on tissue response, wound healing, and pain following periodontal crown lengthening surgery— a clinical study. *Neuroquantology.* 2022;20:3292–301. <https://doi.org/10.48047/NQ.2022.20.22.NQ10327>.
 67. Torul D, Omezli MM, Avci T. Investigation of the clinical efficacy of CGF and ozone in the management of alveolar osteitis: a randomized controlled trial. *Clin Oral Investig.* 2023;27:4521–9. <https://doi.org/10.1007/s00784-023-05074-3>.
 68. Chaudhry K, Rustagi N, Bali R, Khatana S, Kumar S, Kaur A, Kumar P. Efficacy of adjuvant ozone therapy in reducing post-surgical complications following impacted mandibular third-molar surgery: a systematic review and meta-analysis. *J Am Dent Assoc.* 2021;152:842–e8541. <https://doi.org/10.1016/j.adaj.2021.05.006>.
 69. Satapathy A, Balani A, Kharsan V, Karan A, Mazhar H, Awasthy A. Topical-ozonized Olive Oil - A Boon for Post-extraction cases: a Randomized Controlled Trial. *Cureus.* 2023;15:e34478. <https://doi.org/10.7759/cureus.34478>.
 70. Eldien AMS, Hassabou NF. Clinical and cytological assessment of platelet-rich fibrin versus topical ozonated oil in palatal wound healing after free gingival graft harvesting: Randomized controlled trial. *J Oral Maxillofac Surg Med Pathol.* 2022;34:343–51. <https://doi.org/10.1016/j.ajoms.2021.10.006>.
 71. Juber P, Loureiro BB, Zuza EP, Cezario EM, Romeiro RL, Lima-Junior JC, Soares IF, Souza AA. Highly ozonated sunflower oil dose may cause oxidative stress and impact the quality of Life after Palatal Graft removal: secondary endpoints of a Randomized Controlled Clinical Trial. *Ozone-Sci Eng.* 2024;46:144–52. <https://doi.org/10.1080/01919512.2023.2253261>.
 72. Loureiro BB, Juber P, Souza AA, Cezario EM, Lima-Junior JC, Fontes KBFC, Soares IF, Zuza EP. Application of highly ozonated sunflower oil does not improve palatal wound healing: a randomized controlled clinical trial. *J Periodontol.* 2023;94:858–67. <https://doi.org/10.1002/JPER.22-0693>.
 73. Aleksandrina E, Poroykiy S, Makedonova Y, Veremeenko S. Efficacy of ozone therapy in treatment of erosive and ulcerative lesions of oral mucosa. *Archiv EuroMedica.* 2020;10:67–9. <https://doi.org/10.35630/2199-885X/2020/10/2.20>.
 74. Ghorbani F, Yazdaniyan M, Tahmasebi E, Izadi M, Mofid B, Varpaei HA. Effect of ozonated water on oral mucositis and pain induced by head and neck radiotherapy: a cross-sectional study. *Arch Neurosci* 2021;8. <https://doi.org/10.5812/ANS.118914>.
 75. Roopa MC, Jha KA. Study on Ozonized Water in the management of erosive oral Lichen Planus. *Int J Pharm Clin.* 2022;14:241–9.
 76. Veneri F, Filippini T, Bellini P, Console U, Generali L. Ulcerative oral lesions: an overview of non-pharmacologic treatment options. *Acta Biomed Atenei Parmensis.* 2024;95:e2024080. <https://doi.org/10.23750/abm.v95i3.15694>.
 77. Veneri F, Bardellini E, Amadori F, Conti G, Majorana A. Efficacy of ozonized water for the treatment of erosive oral lichen planus: a randomized controlled study. *Med Oral* 2020;e675–82. <https://doi.org/10.4317/medoral.23693>.
 78. Condori JY, Meza-Mauricio J, Mendoza-Azpur G, Castro-Rodríguez Y. Is the Use of Ozonated Oil Effective in the treatment of oral lesions? Systematic review of Clinical studies. *Odovtos-Int J Dent Sc.* 2024;26:35–53. <https://doi.org/10.15517/ijds.2023.57060>.

79. Kumar A, Srivastava A, Sah N, Sah S, Nair VIN, Das A, Singh AK. Evidence-based effectiveness of ozone therapy in the treatment for oral lichen planus - A systematic review. *Natl J Maxillofac Surg.* 2024;15:18–22. https://doi.org/10.4103/njms.njms_20_23.
80. Celakil T, Muric A, Gökcen Roehlig B, Evlioglu G. Management of pain in TMD patients: bio-oxidative ozone therapy versus occlusal splints. *Cranio.* 2019;37:85–93. <https://doi.org/10.1080/08869634.2017.1389506>.
81. Hassan TA, Suhail ZA. The efficacy of Ozonized Water Versus Ringer Lactate Arthrocentesis for the Treatment of Temporomandibular Joint Internal Derangement. *J Craniofac Surg.* 2023;34:e238–41. <https://doi.org/10.1097/SCS.000000000000090>.
82. Özalp Ö, Yıldırım N, Sindel A, Altay MA, Kişniçi RŞ. Evaluation of the short-term efficacy of transdermal ozone therapy in Turkish patients with internal derangement of the temporomandibular joint. *Pesqui Bras Odontopediatria Clin Integr* 2019;19. <https://doi.org/10.4034/PBOCI.2019.191.44>.
83. Torres-Rosas R, Marcela Castro-Gutiérrez ME, Flores-Mejía LA, Torres-Rosas EU, Nieto-García RM, Argueta-Figueroa L. Ozone for the treatment of temporomandibular joint disorders: a systematic review and meta-analysis. *Med Gas Res.* 2023;13:149–54. <https://doi.org/10.4103/2045-9912.345174>.
84. D'Amario M, Di Carlo M, Jahjah A, Mauro S, Natale S, Capogreco M. Ozone and laser effects on dentin hypersensitivity treatment: a Randomized Clinical Study. *J Endod.* 2024;50:554–61. <https://doi.org/10.1016/j.joen.2024.02.007>.
85. Rupel K, Ottaviani G, Bogdan Preda MT, Poropat A, Gobbo M, DI Lenarda R, Biasotto M. Ozone treatment combined with sodium fluoride for the treatment of dentin hypersensitivity: an exploratory study. *Minerva Dent Oral Sci.* 2023. <https://doi.org/10.23736/S2724-6329.23.04830-1>.
86. Matys J, Jaszczak E, Flieger R, Kostrzewska-Kaminiarz K, Grzech-Leśniak K, Dominiak M. Effect of ozone and diode laser (635 nm) in reducing orthodontic pain in the maxillary arch—a randomized clinical controlled trial. *Lasers Med Sci.* 2020;35:487–96. <https://doi.org/10.1007/s10103-019-02896-0>.
87. Nicita F, Calapaj M, Alibrandi S, Donato L, Aquilio E, D'Angelo R, Sidoti A. Efficacy of an experimental gaseous ozone-based sterilization method for clear aligners. *Angle Orthod.* 2024;94:194–9. <https://doi.org/10.2319/061623-421.1>.
88. Purohit H, Pisulkar SK, Kambala SS, Kambala SS, Godbole SD, Dahihandekar C, Mistry RA. Comparative evaluation of disinfection on elastomeric impression material using 2% glutaraldehyde, ultra violet radiation and gaseous ozone using customised disinfection unit—an in-vitro study. *Indian J Forensic Med Toxicol.* 2021;15:192–9. <https://doi.org/10.37506/ijfmt.v15i3.15303>.
89. Wezgowiec J, Paradowska-Stolarz A, Malysa A, Orzeszek S, Seweryn P, Wieckiewicz M. Effects of various disinfection methods on the material properties of silicone dental impressions of different types and viscosities. *Int J Mol Sci* 2022;23. <https://doi.org/10.3390/ijms231810859>.
90. Carvalho RR, Carlos N, De Campos F, Turssi C, Vieira Júnior W, Do Amaral F, Basting R. Ozone gas therapy for tooth bleaching preserves enamel microhardness, roughness and surface morphology. *Acta Odontol Latinoam.* 2023;36:15–23. <https://doi.org/10.54589/aol.36/1/15>.
91. Ferreira Neves Dias T, Ferreira de Campos FU, Turssi CP, Botelho do Amaral FL, Gomes França FM, Basting RT. Color change after tooth bleaching with ozone and 10% ozonized carbamide peroxide for in-office use. *Med Gas Res.* 2022;12:100–6. <https://doi.org/10.4103/2045-9912.330693>.
92. Yuca Y, Yucesoy T, Tok OE, Alkan A. The efficiency of ozone therapy and low-level laser therapy in rat facial nerve injury. *J Craniofac Surg.* 2020;48:308–14. <https://doi.org/10.1016/j.jcms.2020.01.017>.
93. Ameyaroy DK, Ramabhadran BK, Emmatty R, Paul TP, Jose P. Comparative evaluation of the effect of ozone therapy and photodynamic therapy in non-surgical management of chronic periodontitis: a split mouth longitudinal study. *J Indian Soc Periodontol.* 2020;24:447–53. https://doi.org/10.4103/jisp.jisp_381_19.
94. Greenland S, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, Altman DG. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol.* 2016;31:337–50. <https://doi.org/10.1007/s10654-016-0149-3>.
95. Rothman KJ. The origin of modern epidemiology, the book. *Eur J Epidemiol.* 2021;36:763–5. <https://doi.org/10.1007/s10654-021-00790-0>.
96. Rothman KJ. Disengaging from statistical significance. *Eur J Epidemiol.* 2016;31:443–4. <https://doi.org/10.1007/s10654-016-0158-2>.
97. Wasserstein RL, Lazar NA. The ASA Statement on *p*-Values: context, process, and purpose. *Am Stat.* 2016;70:129–33. <https://doi.org/10.1080/00031305.2016.1154108>.
98. Seydanur Dengizek E, Serkan D, Abubekir E, Aysun Bay K, Onder O, Arife C. Evaluating clinical and laboratory effects of ozone in non-surgical periodontal treatment: a randomized controlled trial. *J Appl Oral Sci.* 2019;27:e20180108. <https://doi.org/10.1590/1678-7757-2018-0108>.
99. Cosola S, Giammarinaro E, Genovesi AM, Pisante R, Poli G, Covani U, Marconcini S. A short-term study of the effects of ozone irrigation in an orthodontic population with fixed appliances. *Eur J Paediatr Dent.* 2019;20:15–8. <https://doi.org/10.2380/4/ejpd.2019.20.01.03>.
100. Uslu MÖ, Akgül S. Evaluation of the effects of photobiomodulation therapy and ozone applications after gingivectomy and gingivoplasty on postoperative pain and patients' oral health-related quality of life. *Lasers Med Sci.* 2020;35:1637–47. <https://doi.org/10.1007/s10103-020-03037-8>.
101. Sandra VKV, Shaik Z, Simhadri G, Obili Govindu Gari LR, Sidamreddy BP, Makem N. Comparison of laser therapy and ozonated water on gingival inflammation in orthodontic patients with fixed appliances. *J Clin Transl Res.* 2021;7:625–30.
102. Bansode P, K S, Muralidharan DS. Effectiveness of Ozonated Water on Gingivitis: a systematic review. *Cureus.* 2024;16:e61006. <https://doi.org/10.7759/cureus.61006>.
103. Kaur A, Bhavikatti SK, Das SS, Khanna S, Jain M, Kaur A. Efficacy of Ozonised Water and 0.2% chlorhexidine gluconate in the management of chronic Periodontitis when used as an irrigant in conjunction with phase I therapy. *J Contemp Dent Pract.* 2019;20:318–23.
104. Mehrotra R, Gupta S, Siddiqui ZR, Chandra D, Iqbal SA. Clinical efficacy of ozonated water and photodynamic therapy in non-surgical management of chronic periodontitis: a clinico-microbial study. *Photodiagnosis Photodyn Ther.* 2023;44:103749. <https://doi.org/10.1016/j.pdpdt.2023.103749>.
105. Boguski T. Understanding units of measurement. *Environ Sci Technol Briefs Citizens.* 2006;2:1–2.
106. Sega A, Zanardi I, Chiasserini L, Gabbriellini A, Bocci V, Travagli V. Properties of sesame oil by detailed ¹H and ¹³C NMR assignments before and after ozonation and their correlation with iodine value, peroxide value, and viscosity measurements. *Chem Phys Lipids.* 2010;163:148–56. <https://doi.org/10.1016/j.chemphyslip.2009.10.010>.
107. Valacchi G, Zanardi I, Lim Y, Belmonte G, Miracco C, Sticozzi C, Bocci V, Travagli V. Ozonated oils as functional dermatological matrices: effects on the wound healing process using SKH1 mice. *Int J Pharm.* 2013;458:65–73. <https://doi.org/10.1016/j.ijpharm.2013.09.039>.