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Ozone – mechanism of action, application in treatment of Caries lesions and Endodontics

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Abstract

Ozone therapy is a method used for treatment and prevention across various areas of general and dental medicine. Ozone therapy has a well-substantiated biological mechanism (the Keap1/Nrf2–GSH axis) which, at low, controlled doses, triggers an adaptive antioxidant response and yields antimicrobial, anti-inflammatory, and biostimulatory effects. In cariesology, ozone effectively reduces the microbial load in demineralized dentin (including resistant strains such as E. faecalis and C. albicans), supports remineralization, and increases enamel microhardness.
In endodontics, ozone complements standard root canal disinfection, penetrates hard-to-reach areas, and can support regenerative processes; under controlled parameters it stimulates the proliferation and osteo-/chondrogenic differentiation of hDPSCs.
In summary, when appropriately dosed and indicated, ozone therapy is a promising, biologically active adjuvant with strong potential in regenerative dental medicine and infection control—provided that parameters are strictly controlled and the approach is integrated into evidence-based clinical protocols.endodontics

Keywords: ozone therapy, antimicrobial activity, dental pulp stem cells, endodontic treatment, caries management, antimicrobial, mineralization

Background

Ozone therapy is a method used for treatment and prevention in various fields of general and dental medicine. Due to its antibacterial, anti-inflammatory, and immunostimulatory properties, it is applied in the management of carious lesions, inflammatory diseases of the dental pulp and periodontium, and other oral conditions.
The present review discusses the mechanism of action of ozone and its applications in cariesology and endodontics.

Review Results

Ozone – Essence and Mechanism of Action

Ozone (O_3) is a triatomic, highly reactive form of oxygen characterized by strong chemical activity and a short biological half-life. In nature, it is formed in the upper layers of the atmosphere under the influence of ultraviolet radiation and during electrical discharges in thunderstorms. In medical and dental practice, ozone is artificially generated by specialized devices that convert oxygen (O_2) into ozone through an electric discharge (1,2,3).

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When ozone comes into contact with the cell membrane and surrounding fluid, it does not penetrate deeply into the cell but primarily reacts with water and lipids on its surface. This interaction leads to the formation of reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2) and various transient oxidized compounds known as ozonides. These molecules are sufficiently stable to cross the cell membrane and reach the cytoplasm, where they initiate a cascade of intracellular reactions (4,5).

In the cytoplasm, the protein Keap1 (Kelch-like ECH-associated protein 1) acts as a sensor of oxidative stress. It is bound to another protein, Nrf2 (Nuclear factor erythroid 2-related factor 2), and under normal conditions keeps it in an inactive state. When small amounts of ROS appear, specific chemical groups in Keap1 undergo oxidation, leading to structural changes. This weakens the bond between the two proteins, allowing Nrf2 to be released (4,5,6,7).

The released Nrf2 passes through the nuclear membrane and enters the nucleus, where it binds to specific DNA regions known as antioxidant response elements (AREs). This binding activates a cascade of genes encoding the synthesis of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR). At the same time, the cell increases the production of glutathione (GSH)—its main intracellular antioxidant (5,6).

Role of Glutathione (GSH) in the Cellular Response to Ozone

Glutathione (GSH) is the principal intracellular antioxidant and a key component of the cell's defense mechanism against oxidative stress. It is a tripeptide composed of three amino acids—glutamic acid, cysteine, and glycine—where the active sulfhydryl (-SH) group neutralizes free radicals and reactive oxygen species (ROS) (4,5,7).

Following short-term ozone exposure, the small amounts of ROS generated stimulate the synthesis of new glutathione through activation of Nrf2-dependent genes. Glutathione participates in the neutralization of peroxides and free radicals, during which it becomes oxidized to glutathione disulfide (GSSG). To restore the antioxidant balance, the enzyme glutathione reductase (GR) converts GSSG back into its reduced form (GSH), using energy derived from nicotinamide adenine dinucleotide phosphate (NADPH). In this reaction, GR employs NADPH as an electron donor to regenerate GSH, thereby maintaining cellular redox homeostasis and antioxidant defense. The cell thus sustains a dynamic equilibrium between the two forms—a process known as the glutathione redox cycle (8).

Elevated GSH levels protect lipids, proteins, and DNA from oxidative damage while supporting the activity of other antioxidant enzymes such as catalase (CAT) and glutathione peroxidase (GPx). As a result, cells remain viable and proliferation is promoted. However, at higher ozone doses, when the amount of ROS exceeds the capacity of the glutathione system, this balance is disrupted, leading to cellular damage and apoptosis. Hence, glutathione functions as a buffer—at low ozone doses it triggers an adaptive, protective response, whereas at high doses it becomes depleted, resulting in oxidative injury (4,5,7,8).

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Effect of Ozone on Apoptosis

Apoptosis is a form of programmed cell death—a physiological process through which the body eliminates damaged or unnecessary cells without inducing inflammation. The application of ozone can influence this process depending on the dose and duration of exposure (7).

At low and controlled concentrations, ozone induces a mild and transient oxidative stimulus that activates antioxidant pathways (mainly through Keap1/Nrf2) and increases glutathione (GSH) levels. This creates a protective environment that stabilizes mitochondria and prevents the activation of apoptotic mechanisms. As a result, the cells maintain their viability and even stimulate proliferation and regeneration (4,5,7,8).

Conversely, at higher doses or with prolonged ozone exposure, the amount of reactive oxygen species (ROS) exceeds the cell's antioxidant capacity. Glutathione levels become depleted, mitochondrial dysfunction occurs, and caspase-dependent pathways leading to apoptosis are activated. Therefore, the cellular response to ozone is dose-dependent—at low concentrations it promotes adaptation and proliferation, whereas at high concentrations it induces cellular damage and death (4,5,7).

Under these conditions, cells not only preserve their viability but also enhance their proliferative potential, suggesting an adaptive response typical of a state of "oxidative eustress." This effect disappears at higher concentrations or longer exposure durations, when the balance between ROS and antioxidant systems is disrupted and mitochondria-mediated apoptosis is triggered. Hence, the findings support the hypothesis that the effect of ozone on dental pulp stem cells (hDPSCs) is both dose- and time-dependent, with low doses exerting biostimulatory effects and high doses showing cytotoxicity (4,7,9,10).

Antibacterial, Anti-inflammatory, and Immunomodulatory Effects of Ozone

Ozone exhibits a strong antimicrobial effect against bacteria, viruses, and fungi. Its mechanism of action is based on the potent oxidative capacity of the O_3 molecule, which reacts with the key structural components of microbial cells. Ozone destroys microorganisms within seconds by damaging their cell membranes. It attacks glycoproteins, glycolipids, lipids, lipoproteins, phospholipids, and amino acids, blocks enzymatic systems, and increases membrane permeability, leading to cell lysis and death (11). As a result, the cellular contents leak out and the microorganism rapidly perishes (3).

Moreover, ozone oxidizes enzymes, nucleic acids (DNA and RNA), and sulfhydryl groups in proteins, which results in enzyme inactivation and disruption of the pathogen's metabolic processes (3,12). In bacteria, this manifests as destruction of the cell wall and membrane integrity, while in fungi, ozone alters the structure of the cytoplasm and mitochondria, inhibiting their growth and reproduction (3,12,13,14).

Viruses are highly susceptible to ozone due to their lipid envelopes, which are easily oxidized. For non-enveloped viruses, ozone reacts with viral capsid proteins and nucleic acids, blocking their ability to bind to host cells. A notable example is the effect of ozone on the SARS-CoV-2 (COVID-19) virus, which it can inactivate within three seconds (1,5).

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Why Ozone Does Not Damage Human Cells.

Unlike microorganisms, human cells possess an effective antioxidant defense system—including enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)—which neutralize reactive oxygen species (ROS) and prevent cellular damage. This explains why, at controlled concentrations, ozone can destroy pathogens without harming host tissues (3,4,7,15).

The antimicrobial potential and cytotoxicity of ozonated water depend on the pH and temperature of the medium. At pH 5 and 4 °C, ozone exhibits the highest stability and concentration in aqueous solution. When used at concentrations between 0.4 and 0.8 ppm, ozonated water produces over 95% reduction in Escherichia coli and complete inactivation of Pseudomonas aeruginosa, Staphylococcus aureus, Enterococcus faecalis, and Candida albicans after only one minute of exposure. Under the same conditions, no cytotoxic effect is observed on human fibroblasts, confirming the biocompatibility of ozone at low concentrations and supporting its use as a safe antimicrobial agent in dental practice (16).

Anti-inflammatory and Immunomodulatory Effects of Ozone

Ozone has been shown to exert anti-inflammatory and immunomodulatory actions. A study by Huth et al. (2007) demonstrated that an ozonated environment inhibits activation of the transcription factor NF-κB in human oral epithelial cells and gingival fibroblasts stimulated with TNF-α. Pre-incubation with ozonated solution prevented IκB-α proteolysis, reduced IL-1β and IL-8 expression, and suppressed NF-κB-dependent transcription without affecting cell viability. The authors concluded that ozonated aqueous solutions may be useful in the treatment of periodontal and periapical inflammatory conditions (1,17).

A comparative study by Huth et al. (2006) evaluated the cytotoxicity of gaseous and aqueous ozone on human oral epithelial and gingival fibroblast cells, compared with established antiseptics—chlorhexidine (CHX), sodium hypochlorite (NaClO), and hydrogen peroxide (H_2O_2). The results showed that gaseous ozone reduced cell viability, whereas the aqueous form (1.25–20 μg/mL) caused no cytotoxic effects and even preserved metabolic activity and structural integrity. In contrast, CHX, NaClO, and H_2O_2 markedly decreased cell viability and increased apoptosis. The authors concluded that aqueous ozone demonstrated the highest biocompatibility among the tested agents and can be safely used in dental applications (12).

Applications of Ozone

Due to its strong oxidative properties, ozone exhibits pronounced antimicrobial, anti-inflammatory, and biostimulatory effects, which underpin its wide range of applications in medicine. It can be used in various forms—gaseous ozone, ozonated water, ozonated saline, or ozonated oils—depending on the therapeutic goal and the type of tissue being treated (1,3,8).

In dental medicine, ozone has applications in cariology, endodontics, periodontology, mucosal lesion therapy, prosthodontics, and oral surgery. Its effectiveness relies on the ability to eliminate pathogenic microorganisms while simultaneously improving oxygenation and metabolic activity in the affected tissues (1).

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Ozone Applications in Caries Management

Microorganisms are a major etiological factor in the destruction of hard dental tissues. Therefore, the antibacterial properties of ozone play a key role in reducing the microbial count in carious dentin lesions (18). Studies of the microbial flora in approximal carious lesions have shown substantial species diversity. The microbial population, together with dentin debris, saliva, and blood residues, forms a so-called contaminated smear layer which, if not removed or disinfected, may persist beneath restorations and predispose to secondary caries. For this reason, disinfection of the dentin surface with antibacterial agents is essential before restoration (19,20).

Our clinical investigations demonstrated that treatment with hydrogen peroxide alone destroyed pathogenic microorganisms in carious dentin by only about 20%. In contrast, application of ozone for 24 seconds resulted in complete eradication of microorganisms. The isolated strains included Streptococcus mutans, Candida albicans, Enterococcus faecalis, Peptostreptococcus spp., and Actinomyces naeslundii—notably, even the highly resistant Enterococcus faecalis and Candida albicans were completely eliminated after ozone exposure (19).

Other authors have also confirmed that ozone effectively inactivates Streptococcus. mutans, Lactobacillus acidophilus, A. naeslundii, and Candida albicans within seconds, without damaging surrounding tissues. Their findings indicate that when properly dosed, ozone is biocompatible, non-toxic, and suitable as an adjuvant agent in the prevention and treatment of dental infections (21).

Treatment of deep carious lesions in primary teeth using a minimally invasive protocol involving partial caries removal and ozone application (HealOzone™, 60 s) achieved a 93.6% clinical success rate, defined as absence of recurrent caries and preservation of pulp vitality (20).

Effect of Ozone on Enamel

An interesting study by Celiberti et al. (2006) investigated the influence of ozone on the physical properties of enamel. The authors found that short-term ozone exposure caused temporary dehydration and an increase in enamel microhardness, an effect that normalized after rehydration. No permanent alterations were observed in surface morphology or adhesive properties, confirming the safety of ozone application prior to etching and fissure sealing (22).

Ozone can therefore be regarded as a minimally invasive and effective therapeutic alternative for the prevention and management of early carious lesions (3,19,20). A study by Kirilova and Kirov reported that application of ozone gas to hard dental tissues over ten sessions significantly reduced the formation of new carious lesions over a two-year period in caries-active individuals (11).

Similarly, Floare et al. (2022) demonstrated that ozone stimulates enamel remineralization and improves its microstructure without causing structural damage (13,14,23).

Effect of Ozone on Dentin

Application of ozone to dentin surfaces induces a series of physicochemical changes that promote remineralization and disinfection of the hard dental tissues. Ozone oxidizes the organic components of demineralized dentin and removes residual bacterial products, thereby facilitating the cleaning of dentinal tubules and reducing microbial load. Additionally, ozone enhances the diffusion of calcium, phosphate, and fluoride ions from saliva into the surface of the affected dentin

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and neutralizes acidic proteins produced by cariogenic bacteria. These reactions promote mineral deposition and increase the degree of dentinal tubule occlusion (8).

Application of Ozone in the Treatment of Pulp and Periodontal Diseases

Due to its strong oxidative potential and ability to penetrate deeply into the dentinal tubules, ozone provides an effective antibacterial effect within the root canal system, including hard-to-reach areas where traditional irrigants have limited efficacy. Ozone also exerts a biostimulatory effect on pulp and periapical cells, promoting tissue regeneration and healing (8).

It has been demonstrated that application of ozone gas through a chlorhexidine solution within the root canal system successfully eliminates Enterococcus faecalis during the treatment of chronic apical periodontitis (12,24,25).

Effect of Ozone on Human Stem Cells

The observed biological effects of ozone have raised interest regarding its action on dental pulp and stem cells residing within it. According to Sagai & Bocci (2011) and Tricarico & Travagli (2021), at optimal concentrations, ozone acts as a biomodulator, inducing a mild and transient oxidative stimulus. As a result, cells maintain a stable redox balance, higher metabolic activity, and enhanced regenerative capacity (4,7).

An investigation into the cytotoxicity of various concentrations of ozonated water (2, 4, 8, and 16 mg/L) on human pulp cells isolated from deciduous teeth provided noteworthy results (10). Using the MTT assay, the authors reported that all tested concentrations were biocompatible, while the lowest doses (2 mg/L and 4 mg/L) even induced cell proliferation without any cytotoxic signs. At 2 mg/L, the highest cell viability and a stable proliferative effect were observed up to 48 hours, supporting the hypothesis that low ozone concentrations stimulate cellular activity through mild oxidative signaling. These findings confirm the potential of ozonated water as a biocompatible irrigant and a possible adjuvant agent in regenerative endodontics (10).

Effect of Ozone on Human Dental Pulp Stem Cells

In another study, Pasalkar et al. (2022) treated human dental pulp stem cells (hDPSCs) with gaseous ozone at low concentrations (~10 μg/mL). The authors observed a moderate increase in cell proliferation and enhanced osteogenic and chondrogenic differentiation, while adipogenic differentiation was suppressed. These effects were attributed to the selective activation of ROS-dependent signaling pathways, which regulate genes involved in osteogenesis and the cellular antioxidant response (9).

These findings confirm that, under controlled conditions, ozone can act as a regulator of hDPSCs, promoting proliferation and directing the differentiation potential of these cells toward osteogenic and chondrogenic lineages. This makes ozone therapy a promising adjuvant approach in regenerative endodontics and tissue engineering of the pulp–dentin complex, where the goal is to restore the biological function of the dental pulp and stimulate the formation of new dentin. Further studies in this direction are warranted.

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Side Effects of Ozone

Despite its proven antimicrobial and biostimulatory properties, ozone may exhibit cytotoxic effects when used at excessive concentrations or for prolonged exposure times. High ozone doses induce intense oxidative stress that exceeds the antioxidant capacity of cells, leading to damage of lipids, proteins, and nucleic acids. Consequently, mitochondrial dysfunction, glutathione (GSH) depletion, and activation of caspase-dependent apoptotic pathways occur, resulting in increased apoptosis or necrosis (5,7).

Improper clinical application of ozone may cause irritation of the respiratory tract or eyes, particularly when performed without adequate aspiration or ventilation. Therefore, ozone must be administered at strictly controlled doses and under regulated exposure parameters to avoid toxicity risks. At therapeutic concentrations, ozone does not cause damage to skin or mucosal tissues; on the contrary, controlled application can enhance tissue repair, improve microcirculation, and accelerate healing of superficial wounds (26).

However, high doses or prolonged exposure may lead to transient erythema, dryness, or mild irritation due to lipid oxidation in the superficial epidermal layer. These reactions are temporary and are not associated with deeper tissue injury (4). According to Bocci (2005), when properly dosed, ozone does not induce cellular toxicity in healthy epithelium and even stimulates local oxygenation and bioregeneration (26).

Conclusion

Ozone therapy has a well-substantiated biological mechanism (the Keap1/Nrf2–GSH axis) which, at low, controlled doses, triggers an adaptive antioxidant response and yields antimicrobial, anti-inflammatory, and biostimulatory effects. In cariology, ozone effectively reduces the microbial load in demineralized dentin (including resistant strains such as E. faecalis and C. albicans), supports remineralization, and increases enamel microhardness.

In endodontics, ozone complements standard root canal disinfection, penetrates hard-to-reach areas, and can support regenerative processes; under controlled parameters, it stimulates the proliferation and osteo-/chondrogenic differentiation of hDPSCs.

In summary, when appropriately dosed and indicated, ozone therapy is a promising, biologically active adjuvant with strong potential in regenerative dental medicine and infection control—provided that parameters are strictly controlled and the approach is integrated into evidence-based clinical protocols.

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