



DOSSIER · THERAPY

Ozone Therapy

Ozone therapy is one of the most extensively studied complementary medical procedures. The database reveals a broad but methodologically heterogeneous body of evidence. The most notable finding: the majority of controlled studies focus on the **musculoskeletal system**, while other areas of application show significantly less evidence.

1,042

STUDIES IN
TOTAL

645

IN HUMANS

214

OF WHICH
CONTROLLED

20

IN ANIMALS

64

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

Ozone Therapy at a Glance

ORIGIN:

Ozone therapy is a medical procedure in which a mixture of oxygen (O₂) and ozone (O₃) is used in various forms of application.

STUDY LANDSCAPE:

369 evaluated works · 76 controlled human studies · 145 observational studies · 18 review articles · 6 animal studies · 9 cell culture studies

STRONGEST EVIDENCE:

- Musculoskeletal system: Controlled, randomised studies demonstrate efficacy in acute back pain with herniated discs (double-blind, 2009) and knee osteoarthritis (compared with hyaluronic acid, 2017/2018/2020/2023).
- Wound healing: Non-invasive ozone therapy promotes healing of diabetic foot ulcers in randomised studies (2014) and shows benefits in systematic reviews (2018).
- Periodontology: Ozonated gels are comparably effective to chlorhexidine in randomised studies (2021/2022/2023) for chronic periodontitis and peri-implantitis, with anti-inflammatory effects.
- Safety: Systematic data on tolerability are robust, particularly for local applications (e.g., intra-articular), although side effects such as injection pain are rarely systematically recorded.
- Oxidative stress: Preclinical studies in cell cultures and animal models suggest potential immunomodulatory and antioxidant effects, e.g., in chemotherapy-induced neuropathy (2021), but these findings have not been investigated in human clinical trials.

LIMITATIONS:

- Viral infections/autoimmune diseases: Controlled human studies are lacking; existing data derive from cell cultures, animal models, or small observational studies without consistent results.
- Cancer adjunct therapy: No controlled human studies; existing work consists of case series or basic research without clinical conclusions.
- Long-term effects: Studies are limited to short observation periods (weeks to months); data on safety and efficacy with repeated use are still emerging.

CLASSIFICATION:

Ozone therapy shows consistent evidence for the musculoskeletal system, particularly for joint pain and osteoarthritis, while other applications such as viral infections or cancer adjunct therapy are scarcely supported by controlled studies and require further investigation.

1. What Ozone Therapy Is

Ozone therapy is a medical procedure in which a mixture of **oxygen (O₂)** and **ozone (O₃)** is used in various forms of application. Ozone is a highly reactive gas that occurs naturally through UV radiation or electrical discharges. In therapy, it is mostly produced by medical ozone generators from pure oxygen. Application may be local (e.g., intra-articular, intradiscal, topical) or systemic (e.g., via autologous blood treatment or rectal insufflation). Historically, the method originates from observations in water treatment, where ozone was used for disinfection. The first medical applications date back to the early 20th century, though systematic studies only followed from the 1990s onwards.

Crucial for understanding the study landscape is the **diversity of application forms** and **dosages**. Ozone is used in varying concentrations (typically in the microgram range) and volumes, which complicates direct comparisons between studies. Additionally, **target tissues** vary widely: while local applications (e.g., injections into joints or intervertebral discs) aim for direct effects in the treated area, systemic methods target **immunomodulatory** or **antioxidant** responses. Measuring ozone concentration in tissue is methodologically challenging, so many studies rely on **clinical endpoints** (pain, function) or **surrogate parameters** (inflammatory markers, wound healing).

2. How Robust the Research Is

Research on **ozone therapy** spans several areas of application, with the **musculoskeletal system** being by far the most frequently studied. A significant portion of controlled human studies focuses on **joint pain**, **herniated discs**, or **osteoarthritis**, followed by studies on **safety** and **anti-inflammatory effects**. Further areas of focus include **wound healing** (particularly diabetic foot ulcers) and **periodontal diseases**. Notably, there is a **low number of controlled studies** on other indications such as **metabolic disorders** or **intestinal diseases**, despite these being frequently promoted in practice. Most studies have been published in the last 15 years, with a marked increase since 2015.

Methodologically, the field exhibits **strengths and weaknesses**. Strengths include **some randomised, placebo-controlled studies** with high citation rates, particularly for **back pain** and **knee osteoarthritis**. These studies often feature **double-blind designs** and compare ozone with established treatments such as **hyaluronic acid** or **chlorhexidine**. However, there are also **limitations**: many studies have **small sample sizes**, and **long-term data** are limited. Furthermore, **standardised protocols** for dosage and application are often lacking, which restricts **reproducibility**. Systematic reviews and meta-analyses arrive at **contradictory conclusions**, particularly when assessing **efficacy compared to placebo**. **Safety data** are generally robust, but local side effects (e.g., injection-site pain) are rarely systematically recorded.

Distribution of controlled human studies by area of application — the numbers are not additive, as a single study may be assigned to multiple areas:

AREA OF APPLICATION	CONTROLLED STUDIES
Musculoskeletal system	27

AREA OF APPLICATION	CONTROLLED STUDIES
Safety and tolerability	27
Inflammatory processes	20
Bone and joints	18
Immune system	15
Oxidative stress	11
Skin	11
Fatigue and stress	9

Ozone Therapy: Efficacy or Placebo Effect?

A central challenge in ozone therapy research is the
DIFFICULTY IN DISTINGUISHING SPECIFIC EFFECTS FROM NON-SPECIFIC RESPONSES

. Many controlled studies show **clinical improvements** in both the treatment and placebo groups, with differences often being **minor**. Particularly for **subjective endpoints** such as **pain** or **fatigue**, the **placebo effect** is difficult to control. Additionally, many studies lack **active comparator groups** with established therapies, complicating the interpretation of results. For example: studies on **knee osteoarthritis** frequently compare ozone with **hyaluronic acid**, but not with **physiotherapy** or **analgesics**, despite these being standard in clinical practice.

Another methodological issue is the
LACK OF STANDARDISATION IN OZONE APPLICATION

. Even within a single field of application (e.g., **herniated discs**), **concentration**, **volume**, and **frequency** of injections vary widely. This results in even **meta-analyses** being able to make only **limited statements** about the **optimal dosage**. Furthermore, **surrogate parameters** such as **inflammatory markers** are often used as proof of efficacy without establishing a **causal relationship** to the clinical course. Particularly in **systemic applications** (e.g., autologous blood therapy), it remains unclear whether the measured **antioxidant effects** are actually associated with an **improvement in symptoms**.

3. What Is Often Claimed—and What the Data Show

STATEMENT	EVIDENCE
Ozone therapy for viral infections	The data is still emerging. While there are theoretical models on immunomodulatory effects , controlled human studies are almost entirely lacking. Most research
Systemic ozone therapy for autoimmune diseases	Here, observational studies with small sample sizes predominate. Controlled studies are rare, and the results are inconsistent . Causal evidence is lacking.
Ozone therapy as an adjunctive cancer treatment	There are no controlled studies in humans. The few available works are case series or basic research , which do not permit conclusions regarding clinical appli
Long-term use in chronic conditions	Most studies have short observation periods (weeks to a few months). Data on long-term effects or safety with repeated use are limited.

4. The Most Robust Studies

Ranked by strength of evidence, not by prominence. The full evaluation includes significantly more studies; only the most reliable are listed here.

Controlled Human Trials

- ¹ Intramuscular oxygen-ozone therapy in the treatment of acute back pain with lumbar disc herniation: a multicentre, randomised, double-blind, clinical trial (2009)

- ² Increased growth factors play a role in wound healing promoted by noninvasive oxygen-ozone therapy in diabetic patients with foot ulcers (2014)
- ³ Comparison between intra-articular ozone and placebo in the treatment of knee osteoarthritis: A randomised, double-blinded, placebo-controlled study (2017)
- Ozone therapy for the treatment of chronic wounds: A systematic review (2018)
- Ozonised gels vs chlorhexidine in non-surgical periodontal treatment: A randomised clinical trial (2024)
- The hierarchy of different treatments for myogenous temporomandibular disorders: A systematic review and network meta-analysis of randomised clinical trials (2022)
- ⁴ Intra-articular ozone or hyaluronic acid injection: Which one is superior in patients with knee osteoarthritis? A 6-month randomised clinical trial (2018)
- ⁵ Long-term effects of intra-articular oxygen-ozone therapy versus hyaluronic acid in older people affected by knee osteoarthritis: A randomised single-blind trial (2020)
- ⁶ Ozone Therapy versus Hyaluronic Acid Injections for Pain Relief in Patients with Knee Osteoarthritis: Preliminary Findings on Molecular and Clinical Outcomes (2023)
- Ozone Gel in Chronic Periodontal Disease: A Randomised Clinical Trial on the Anti-Inflammatory Effects of Ozone Application (2021)
- Modulation by Ozone Therapy of Oxidative Stress in Chemotherapy-Induced Peripheral Neuropathy: The Background for a Randomised Clinical Trial (2021)
- Extracorporeal blood oxygenation and ozonation (EBOO): a controlled trial in patients with peripheral artery disease (2005)
- ⁷ Intradiscal oxygen-ozone chemonucleolysis versus microdiscectomy for lumbar disc herniation radiculopathy: a non-inferiority randomised controlled trial (2022)
- The Effect of Gaseous Ozone Therapy in Conjunction with Periodontal Treatment on Glycated Haemoglobin Level in Subjects with Type 2 Diabetes Mellitus: A Randomised Clinical Trial (2020)
- The Effect of Ozone (O₃) versus Hyaluronic Acid on Pain and Function in Patients with Knee Osteoarthritis: A Systematic Review and Meta-Analysis (2020)
- [Effectiveness of ozone therapy compared to other therapies for low back pain: a systematic review with meta-analysis of randomised clinical trials] (2019)
- Ozonised hydrogels vs. 1% chlorhexidine gel for the clinical and domiciliary management of peri-implant mucositis: a randomised clinical trial (2023)
- ⁸ Comparison of ozonated olive oil and chlorhexidine gel as an adjunct to non-surgical periodontal therapy for the treatment of chronic periodontitis: a (2022)
- ⁹ Effects of ozone applied by spinal endoscopy in patients with chronic pain related to failed back surgery syndrome: a pilot study (2013)
- ¹⁰ Effect of ozonated oil and chlorhexidine gel on plaque-induced gingivitis: a randomised controlled clinical trial (2016)
- Effect of high-frequency bio-oxidative ozone therapy for masticatory muscle pain: a double-blind randomised clinical trial (2017)
- ¹¹ Intra-articular injections of ozone versus hyaluronic acid for knee osteoarthritis: a level I meta-analysis (2024)
- Evaluation of ozone therapy in endodontic treatment of teeth with necrotic pulp and apical periodontitis: a randomised clinical trial (2021)
- Comparison of ultrasound-guided subacromial corticosteroid and ozone (O₂-O₃) injections in the treatment of chronic rotator cuff (2023)

5. Summary

Ozone therapy is one of the more extensively studied complementary medical procedures, with the most robust evidence supporting its use for the musculoskeletal system—particularly in joint pain, herniated discs, and osteoarthritis. Some controlled, randomised studies demonstrate clinical improvements, often in comparison with established treatments such as hyaluronic acid or chlorhexidine. Promising data also exist in wound healing (e.g., diabetic foot ulcers) and periodontology, suggesting anti-inflammatory and tissue-regenerative effects. Safety data are generally robust, though local side effects such as injection pain are rarely systematically documented. Methodologically, however, the studies are heterogeneous: small sample sizes, lack of standardisation in dosage and application, and short observation periods limit the strength of the evidence. Additionally, active comparator groups using established therapies (e.g., physiotherapy, analgesics) are often absent, complicating the interpretation of results.

HYPOTHESIS Ozone therapy may hold potential for chronic inflammatory conditions due to its immunomodulatory and antioxidant properties, but the current evidence base is limited. Particularly in systemic applications (e.g., autologous blood therapy), it remains unclear whether the measured effects on oxidative stress correlate with clinical improvements. **Hypothesis:** The efficacy for subjective endpoints such as pain or fatigue may be strongly influenced by the placebo effect, as many studies show only minor differences between the verum and placebo groups. **Hypothesis:** Combining ozone therapy with other treatment modalities (e.g., physiotherapy) could yield synergistic effects, but this has scarcely been investigated. The lack of standardisation in application methods further hinders reproducibility and comparability of results.

To improve the evidence base, large-scale, multicentre studies with standardised protocols for dosage, application, and observation periods are necessary. Particularly urgent are long-term studies examining safety and efficacy with repeated use, as well as trials incorporating active comparator groups (e.g., physiotherapy, established medications). Furthermore, the underlying mechanisms at the cellular level require further investigation to clarify causal relationships between oxidative effects and clinical outcomes. For applications outside the musculoskeletal system (e.g., autoimmune diseases, viral infections), controlled human studies are lacking, which would enable a well-founded assessment. Finally, the development of biomarkers to objectively measure ozone's effects in tissue would be desirable.

6. Unresolved Questions

- **Dosage:** Which ozone concentrations and application methods are optimal for which indications?
- **Mechanism:** How exactly does ozone act at the cellular level, and which signalling pathways are critical?
- **Combination therapies:** Are there synergistic effects with other treatments (e.g., physiotherapy, medications)?

Frequently Asked Questions

Is ozone therapy for herniated discs an alternative to surgery?

The evidence demonstrates **clinical improvements** in **acute low back pain** caused by herniated discs, particularly in **short-term observations**. However, most controlled studies do not directly compare ozone therapy with **surgical procedures**, but rather with **placebo** or **conservative therapies**. **Non-inferiority** to surgery has **not been established**. Furthermore, **long-term data** on **recurrence rates** or **structural changes** in the intervertebral disc are lacking.

How safe is ozone therapy, and what side effects have been documented?

The **safety data** from controlled studies are **overall robust**, particularly for **local applications** (e.g., intra-articular). Common side effects include **transient pain** at the injection site or **local irritation**. Systemic applications (e.g., autologous blood therapy) **rarely** result in **serious adverse events**, though there are **isolated reports** of **embolisms** or **allergic reactions**. The **evidence on long-term side effects** is limited, as most studies have **short follow-up periods**.

Can ozone therapy be used for diabetic foot ulcers?

There are **controlled studies** demonstrating **accelerated wound healing** in diabetic foot ulcers through **topical ozone applications**. The results are **consistent**, though they are based on **small sample sizes** and **short follow-up periods**. A **comparison with standard therapies** (e.g., moist wound care) is lacking in most studies. The **evidence is insufficient** to recommend ozone as a **first-line therapy**.

Sources

- 1 Intramuscular oxygen-ozone therapy in the treatment of acute back pain with lumbar disc herniation: a multicenter, randomized, double-blind, clinical trial of active and simulated lumbar paravertebral injection
Paoloni M, Di Sante L, Cacchio A, Apuzzo D, Marotta S, Razzano M et al. · 2009
- 2 Increased growth factors play a role in wound healing promoted by noninvasive oxygen-ozone therapy in diabetic patients with foot ulcers
Zhang J, Guan M, Xie C, Luo X, Zhang Q, Xue Y · 2014
- 3 Comparison between intra-articular ozone and placebo in the treatment of knee osteoarthritis: A randomized, double-blinded, placebo-controlled study
Lopes de Jesus CC, Dos Santos FC, de Jesus LMOB, Monteiro I, Sant'Ana MSSC, Trevisani VFM · 2017
- 4 Intra-articular ozone or hyaluronic acid injection: Which one is superior in patients with knee osteoarthritis? A 6-month randomized clinical trial
Raeissadat SA, Rayegani SM, Forogh B, Hassan Abadi P, Moridnia M, Rahimi Dehgolan S · 2018
- 5 Long-term effects of intra-articular oxygen-ozone therapy versus hyaluronic acid in older people affected by knee osteoarthritis: A randomized single-blind extension study
de Sire A, Stagno D, Minetto MA, Cisari C, Baricich A, Invernizzi M · 2020
- 6 Ozone Therapy versus Hyaluronic Acid Injections for Pain Relief in Patients with Knee Osteoarthritis: Preliminary Findings on Molecular and Clinical Outcomes from a Randomized Controlled Trial
Sconza C, Di Matteo B, Queirazza P, Dina A, Amenta R, Respizzi S et al. · 2023
- 7 Intradiscal oxygen-ozone chemonucleolysis versus microdiscectomy for lumbar disc herniation radiculopathy: a non-inferiority randomized control trial
Kelekis A, Bonaldi G, Cianfoni A, Filippiadis D, Scarone P, Bernucci C et al. · 2022
- 8 Comparison of Ozonated Olive Oil and Chlorhexidine Gel as an Adjunct to Nonsurgical Periodontal Therapy for the Treatment of Chronic Periodontitis: A Randomized Controlled Clinical Trial
Nambiar S, Malothu S, Karmakar S, Varkey A, Chandra D, Chava VK · 2022
- 9 Effects of ozone applied by spinal endoscopy in patients with chronic pain related to failed back surgery syndrome: a pilot study
Magalhães FN, Soares SC, Torres JM, Ungaretti A, Cacciaccaro MF, Teixeira MJ et al. · 2013
- 10 Effect of ozonated oil and chlorhexidine gel on plaque induced gingivitis: A randomized control clinical trial
Indurkar MS, Verma R · 2016
- 11 Intra-articular injections of ozone versus hyaluronic acid for knee osteoarthritis: a level I meta-analysis
Migliorini F, Giorgino R, Mazzoleni MG, Schäfer L, Bertini FA, Maffulli N · 2024

International Health Research

Research, put in context. Every statement leads to the original paper; the decision in the individual case rests with the treating professional.
ih-research.com/en/knowledge/ozone-therapy/ · Last updated 2026-10-15