

Ozone therapy for the complementary treatment of diabetic foot ulcer: integrative review

Ozonioterapia para o tratamento complementar da úlcera do pé diabético: revisão integrativa

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ABSTRACT | OBJETIVO: To analyze the knowledge about the use of ozone therapy as a complementary treatment for diabetic foot ulcers. **METHODS:** This is an integrative literature review in which the search for articles took place in the Latin American and Caribbean Health Sciences Literature (LILACS), Medical Literature Analysis and Retrieval System Online (MEDLINE) databases. In addition to these, the Scientific Electronic Library Online (SciELO), National Medical Sciences Information Center of Cuba (CUMED) databases, and the portal for the dissemination of Hispanic scientific production, Dialnet, were also used. **RESULTS:** The research analyzed a sample of seven articles. They were organized into thematic categories according to the content that emerged in the publications: ozone therapy application methods in the treatment of diabetic foot ulcers, the benefits of ozone therapy for diabetic foot ulcers, and limitations of ozone therapy use. **FINAL CONSIDERATIONS:** From the discursive analysis of scientific articles, it is hoped that the results of this study become an incentive tool for the development of further research on the use of ozone therapy as a complementary for diabetic foot ulcers.

KEYWORDS: Ozone therapy. Diabetic Foot. Complementary therapies.

RESUMO | OBJETIVO: Analisar os conhecimentos acerca da utilização da ozonioterapia para o tratamento complementar da úlcera do pé diabético. **MÉTODOS:** trata-se de uma revisão integrativa da literatura, na qual a busca dos artigos ocorreu nas bases de dados Literatura Latino-americana e do Caribe em Ciências da Saúde (LILACS) e Medical Literature Analysis and Retrieval System Online (MEDLINE). Para além destas, utilizaram-se também as bases de dados Scientific Electronic Library Online (SciELO), Centro Nacional de Informação de Ciências Médicas de Cuba (CUMED) e o portal de difusão da produção científica hispânica, Dialnet. **RESULTADOS:** a pesquisa analisou uma amostra de sete artigos. Estes foram organizados em categorias temáticas de acordo com os conteúdos que emergiram das publicações: métodos de aplicação da ozonioterapia no tratamento da úlcera do pé diabético; os benefícios da ozonioterapia para úlcera do pé diabético; e limitações para o uso da ozonioterapia. **CONSIDERAÇÕES FINAIS:** a partir da análise discursiva dos artigos científicos, almeja-se que os resultados deste estudo se tornem uma ferramenta de incentivo para o desenvolvimento de outras pesquisas sobre o uso da ozonioterapia como tratamento complementar da úlcera do pé diabético.

PALAVRAS-CHAVE: Ozonioterapia. Pé Diabético. Terapias Complementares.

Introduction

Brazil is the country with the fourth highest number of diabetes mellitus (DM) cases in the world, with 14.3 million individuals with the disease and with a higher proportion among women.^{1,2} The most common complications related to this disease are eye problems, infections, kidney damage, and frequent skin or mucosal ulcerations on the feet.³ About 15% of individuals with diabetes may develop foot lesions, and their management is complex, especially when there is an associated infection.⁴

Lower extremity complications have been significant in developed countries as well as in developing ones.² The annual incidence of this problem varies between 2% and 4% and is responsible for about 50% to 70% of non-traumatic amputations in patients with DM.⁵ Diabetic foot ulcer complications are one of the most prevalent and difficult to treat, as they include the presence of disorders such as infection, ulceration, and/or soft tissue destruction, associated with neurological changes and various degrees of peripheral arterial disease in the lower limbs.^{3,6} Diabetic foot ulcers can lead to disability for individuals, also significantly affecting their quality of life.⁷

The treatment for the diabetic foot is based mainly on the relief of discomfort and depends on its degree of impairment. In the presence of pain, analgesics are used, and in infection, intravenous antibiotic therapy is. In some cases, surgical intervention is performed, as well as adjuvant techniques.^{1,5}

Therefore, the offer of complementary therapy for this type of lesion has been growing, such as Ozone therapy.⁸ Ozone is a gas that can optimize cellular metabolism and, because of its antioxidant and antibacterial effects, aids in better diabetic foot ulcer healing.⁹

Some studies present the importance of ozone therapy in the treatment of the diabetic foot.^{10,11} A case study described the relation of hydro-ozone therapy associated with topical dressing with oil and ozonated cream in the treatment of pododactyl lesions with severe vascular compromise.¹⁰ The following benefits of this therapy were described: antiseptic action, pain reduction, reduction of necrotic tissue, improved oxygenation, and neovascularization. This contributed to efficient healing within 14 weeks of therapy. Corroborating this therapy, a literature

review with eight articles demonstrated similar benefits in the use of this therapy, highlighting it as promising since the improvement in the aspect of the lesion favors a better quality of life for the patient.¹¹

Ozone therapy has been used since the 19th century and is currently an approved practice in several places around the world, such as in Europe, Asia, and Cuba.¹² Its application in Latin America and the United States has been efficient and promising, helping in the treatment of wounds, especially in diabetic patients.¹³

In Brazil, this practice is among the procedures offered in the Política Nacional de Práticas Integrativas e Complementares em Saúde - PNPICS (National Policy of Integrative and Complementary Health Practices), of the Brazilian Sistema Único de Saúde - SUS (Unified Health System), through Ordinance No. 702, of March 21, 2018, of the Brazilian Ministry of Health.¹⁴ In 2020, the Conselho Federal de Enfermagem - Cofen (Federal Council of Nursing) issued a normative opinion No 001, which recognizes ozone therapy as a complementary therapy that can be performed by trained nurses. To this end, it recommends that these professionals take courses with a minimum course load of 120 hours.¹⁵

Under this aspect, seeking to understand how ozone therapy has demonstrated effectiveness in the treatment of diabetic foot, this study aims to analyze the knowledge about the use of ozone therapy for the complementary treatment of diabetic foot ulcers.

Method

This is an integrative literature review, a research method that aims to synthesize the results obtained in research on an object or issue, in a systematic, organized and comprehensive manner that contributes to the deepening of knowledge on the investigated subject.¹⁶ To prepare this type of study, six distinct steps must be followed: 1) Elaboration of the guiding question; 2) Search of the available literature; 3) Data collection; 4) Critical analysis of the included articles; 5) Discussion of the results; and finally, 6) Synthesis of the review.¹⁷

After choosing the subject, a previous survey of the literature was carried out, which enabled the identification of the problem to be studied and the

elaboration of the guiding question, which consists of: what is the main knowledge about the use of ozone therapy for the complementary treatment of diabetic foot ulcers?

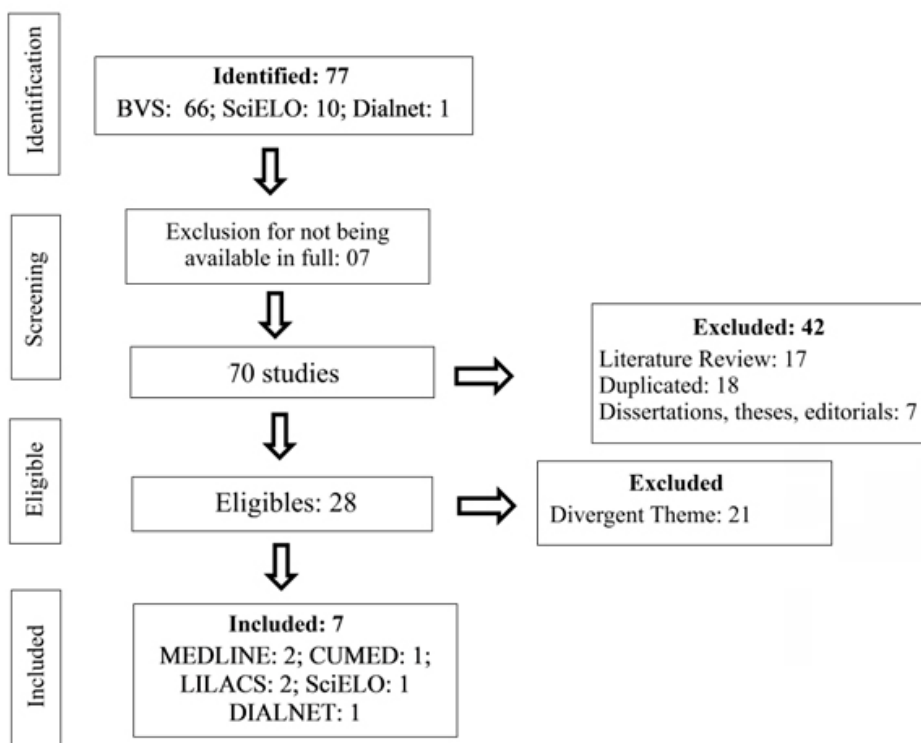
The bibliographic survey was conducted between January and February 2022, by three researchers in the Virtual Health Library (VHL), in the following databases: Latin American and Caribbean Literature on Health Sciences (LILACS) and Medical Literature Analysis and Retrieval System Online (MEDLINE). In addition, the Scientific Electronic Library Online (SciELO), the National Medical Sciences Information Center (CNICM) from Cuba, and the Hispanic scientific production diffusion portal, Dialnet.

The choice of these databases was motivated by the fact that they have national and international publications with impact, a broad search spectrum, and a diversity of indexed journals.

For search strategy, the following Health Science Descriptors (HSD) were used: *ozonioterapia*; *“pé diabético”*; *“terapias complementares”*. These were combined with the Boolean operator “AND” in different ways to allow a broad search. In this sense, the following selection criteria were also adopted: articles in Portuguese, English, and Spanish languages, made available for free, in full, between 2011 and 2021, because they are more recent studies on the subject.

From the strategy used, 77 publications were found, from which those that were not available in full were excluded. The following publications were also excluded from this review: literature reviews, dissertations, theses, editorials, and duplicate publications. At the end of the initial selection, 28 articles were selected for reading of titles and abstracts. Of these, 21 were excluded for presenting divergent subjects. Finally, 7 articles were selected for full reading and later included for analysis and discussion since they met the eligibility criteria established by this research. The article selection process is described in the diagram (Figure 1), according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).¹⁸

Figure 1. Diagram of identification, screening and inclusion of studies



Source: The authors (2022).

Results

From the total of seven articles selected for this review, two (29%) were published in Cuba, one (14%) and each in Brazil, China, Iran, Spain, and Mexico. Regarding language, four (57%) were in Spanish, two (29%) in English, and one (14%) in Portuguese. As for the year of publication, 2014 had the highest number, two (29%), followed by 2015, 2016, 2019, 2020, and 2021, which had the same number of publications, one (14%), in each year. Regarding the type of study, case studies predominated with four (57%), one experimental intervention study (14%), one prospective randomized controlled study (14%), and finally, one retrospective/descriptive study (14%). Table 1 describes the characteristics of the selected publications.

Table 1 . Characteristics of the studies selected for the review. Salvador, BA, Brazil, 2022 (to be continued)

Authors/Year/Country	Type of study	Objective	Main results
1. Zhang et al., 2014/China ¹⁹	Prospective randomized controlled study	To evaluate the effects of ozone therapy on healing and the expressions of vascular endothelial growth factor (VEGF), transforming growth factor- β (TGF- β), and platelet-derived growth factor (PDGF) of diabetic foot wounds in the early phase after treatment.	The effective rate of the ozone group was significantly higher than that of the control group (92% versus 64%, $P < 0.05$). Wound size reduction in the diabetic foot was significantly greater in the ozone group than in the control group ($P < 0.001$).
2. Faraji et al., 2021/Iran ²⁰	Case Study	To describe the treatment of a diabetic foot ulcer using ozone therapy and a silver dressing in a patient who presented dramatic improvement of the post-traumatic wound.	After 1 month of wound treatment with ozone therapy, the patient's foot ulcer had healed, and he was discharged from our wound care service in stable and good general condition.
3. Fabelo-Martínez et al., 2019/Cuba ²¹	Retrospective and descriptive	To determine the evolution of diabetic foot ulcers with mixed treatment of Heberprot P® and ozone therapy.	It was found that patients treated with Heberprot-p® and ozone therapy had a good response to treatment (60.5%), granulation time between 2 and 4 weeks (55.6%), with a predominance of hospitalization between 11 and 21 days.
4. Arizpe, 2016/Spain ²²	Case Study	Report diabetic foot ulcer treatment with a cold ozone probe.	With the application of ozone therapy, the elimination of microorganisms present in the lesion was achieved, as well as the healing of the ulcerated lesion with a complete reduction of symptoms in 5 sessions, but with the elimination of pain since the first application.
5. Marchesini; Ribeiro, 2020/Brazil ²³	Case Study	To verify the effect of ozone therapy on the healing of a chronic wound in a patient with diabetes mellitus.	A 99% reduction in colony-forming units was obtained, and there was a 45.5cm ² reduction in the tissue lesion. Ozone therapy showed a positive result, leading to wound reduction.

Table 1 . Characteristics of the studies selected for the review. Salvador, BA, Brazil, 2022 (conclusion)

Authors/Year/Country	Type of study	Objective	Main results
6. Álvarez-Duarte et al., 2014/Cuba ²⁴	Experimental Intervention Study	To evaluate the benefits of ozone intervention in type 2 diabetic patients suffering from the neuroinfectious diabetic foot.	The frequency of improvement of lesions exceeded 75%, higher in those who received the combined treatment (86%), which did not differ from those who received ozone alone (84%). The mean length of stay for those receiving antibiotics alone (35 days) did not differ from those treated with ozone.
7. Bladinieres-Camara et al., 2015/Mexico ²⁵	Case Study	To report the case of a patient with the diabetic foot with clinical features of neuro-ischemia and previously treated with ozone therapy.	After receiving ozone therapy, resection of the third and fourth fingers was performed due to the extent of the inflammatory process and necrosis. After the surgical treatment, ozone treatment was continued. The patient sought care at the center for not having obtained the offered improvement, noticing a progressive deterioration of the foot and the surgical wound.

Source: The authors (2022).

Discussion

For ample discussion of the articles, they were organized into thematic categories according to the contents that emerged in the publications, namely: 1) Ozone therapy application methods in the treatment of diabetic foot ulcers, 2) The benefits of ozone therapy for diabetic foot ulcers, and 3) Limitations for ozone therapy use.

1) Ozone therapy application methods in the treatment of diabetic foot ulcers

Among the most used methods of application of ozone therapy, it is worth mentioning the use of direct ozone through a bag that uses ozone gas. The topical use of ozone occurs in wounds of the lower and upper limbs due to the anatomy of these limbs, favoring the coupling of the bag, not allowing the escape of ozonated gas.^{26,27} This method becomes very efficient but requires a closed system to restrict the action of the gas in the affected area.²⁶

From the publications analyzed, 71% used ozone topically through a bag as an application method for the treatment of lesions but associated with it, the use of other substances or procedures was identified, such as the bag technique with debridement and conventional dressing. In a study with 50 subjects¹⁹, who were randomized into two groups, after debridement, the ozone group received non-invasive treatment with bag-shaped ozone-oxygen in addition to the standard treatment. The control group received only standard treatment, which included debridement and dressings that were appropriate for exudate levels and maintenance of wound moisture. The effectiveness rate was significantly higher in the ozone group than in the control group, as it showed healing, growth factors, and increased collagen content in the wound.

The ozone combination in a bag form with silver dressing has also been an option for lesions treatment. A study²⁰ that used the bag associated with silver dressing showed excellent results in a patient with an infected ulcer. The patient received a 70 vg/dL ozone dose over 30 days in 10 sessions (one 20-minutes session every three days). Between each session, the wound of the patient was wrapped in gauze bandages impregnated with silver. Due to the rapid growth of granulation tissue, all deep parts of the ulcer were filled. After one month of treatment, the patient was discharged with the ulcer completely healed. Therefore, the authors concluded the efficacy of ozone therapy associated with silver dressing as an adjuvant in diabetic foot ulcer treatment.

Other ozone associations have shown to be effective, such as the mixed treatment with ozone and Heberprot-P, an injectable medication with local application.²⁰ Created in Cuba, this medication in the form of a lyophilized powder, which has Recombinant Human Epidermal Growth Factor in its composition, was diluted in 5 ml of water for injection and applied intralesionally three times a week. It is a drug already used in several countries, but since 2013, it is under study for release in Brazil.²⁸

One study found that most patients who used the mixed treatment with Heberprot-P and ozone therapy had a good response to treatment (60.5%) and a granulation time between 2 and 4 weeks (55.6%), and a hospitalization time of 11 to 21 days.²¹

Firstly, the ozone was administered simultaneously with the Heberprot-P on the same days, three times a week. The Heberprot-P was only administered once the bag containing the ozone was removed. Finally, the authors found favorable results when using the mixed treatment.

The ulcer washing with ozonated water and ozone application with cold plasma activated by an electrical source, iontophoresis, has proven to be a safe, non-invasive technique with good results. A study developed in Spain administered ozone produced with cold plasma to ulcerated lesions on the right hallux, using a glass probe with a combination of noble gas that is activated by an electrical source. When in contact with the tissues, the probe produced an ion discharge through the area, stimulating the oxygen present in the blood at the site of the area to be treated, converting it into ozone.²⁵ The ulcer was washed with ozonated water and the cold plasma probe and ozonated oil were applied to the hallux ulcer. As a result, the pain was eliminated since the first application, the microorganisms present in the lesion were eliminated, and the ulcerated lesion was healed.²⁵

Another combination that has shown excellent results is the ozone administration with local and systemic application, plus the use of antibiotic therapy. Authors conducted an experimental intervention-type study with 150 patients divided into three groups. The first group received ozone in a bag associated with rectal application and

insufflation, which is considered a systemic route. The second group was treated with oral antibiotics only. The third group received ozone and antibiotic treatment. All groups were treated for the same period of 21 days. At the end of the study, the authors found a high percentage of cured patients in each group studied, with the highest rate, 84%, in the group that used the two combined therapies, ozone and antibiotic therapy.²⁴

2) The benefits of ozone therapy for diabetic foot ulcers

Regarding this category, the studies analyzed affirmed that ozone can be used as an adjuvant in conventional therapy since its main function is not to replace drugs but to contribute to the results of clinical and pharmacological treatment²⁰⁻³⁰, being a complementary treatment for diabetic foot ulcers.^{19,31} Publications have shown significant and relevant benefits when using ozone both topically and associated with other treatments, such as benefits regarding the increase of growth factors, a significant reduction, and an accelerated healing process of the lesion.

Corroborating the studies analyzed, other authors who were not selected during the search denote that ozone has great potential in the complementary treatment of diabetic foot ulcers, among other injuries, besides increasing tissue oxygenation, triggering the release of cytokines for tissue repair.³²

A randomized study of 50 patients proved that there was an increase in platelet and cell growth factors, local collagen, and a significant reduction of wound area in the group that received non-invasive oxygen-ozone treatments with 52 g/mL ozone (total volume: 20-50 ml) in a special bag for 30 minutes a day, for 20 days, using the ozone generator device, in addition to standard treatment.¹⁹

Such benefits were also identified in another publication that was not listed during the search according to the selected descriptors. This study analyzed a group of ten patients who received exclusive treatment with ozone bags for the healing of skin ulcers located on the lower limbs. The same study reported a reduction or disappearance of pain, reduction of edema, re-epithelialization, and wound closure.³³

In a study, topical ozone therapy acted by inducing neoangiogenesis, increasing blood flow at the wound site, preventing the proliferation of microorganisms with antiseptic properties, and accelerating the formation of granulation tissue, especially with disinfection and cleaning of the wound, providing tissue adaptation to oxidative stress. These factors, associated with revascularization and surgical interventions, led to complete healing. This report concluded that the use of ozone therapy, associated with conventional therapy, favored diabetic foot ulcer healing because it promoted local oxygenation and accelerated tissue repair.³⁴

Ozone can also be used to eliminate microorganisms in potentially contaminated and infected wounds because it is capable of eliminating all known types of gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa* and *Escherichia coli*, which are resistant to several types of antibiotics.³³ Researchers, through microbiological analysis, identified colonies of *Pseudomonas aeruginosa* (value greater than 100,000/ CFU). After 15 ozone therapy sessions, the value was lower (350 CFU), which evidences a reduction of colonies.²³

Ozone therapy provides other beneficial effects, such as pain reduction due to its analgesic effect and anti-inflammatory action.³⁶ Regarding anti-inflammatory action, ozone has a mechanism of action that acts as an analgesic and anti-inflammatory since it reduces the production of inflammatory mediators that are harmful to the healing process.^{37,38}

The use of ozonated oil has proven to be very effective in reducing the pain and inflammation of venous ulcers in the lower limbs³⁹, since ozone therapy acts on the inflammatory process, with a biological effect related to the inhibition of alpha factor tumor necrosis⁴⁰, which can stimulate the inflammatory response and other cytokines that cause fever and fight infection.⁴¹

Other benefits that have also been observed: the elimination of odor, improvement in the underlying skin, and in hydration and self-esteem. A study carried out with 40 individuals submitted to ozone therapy, after 20 sessions, showed that 32 of them presented a complete recovery of the lesions with incalculable improvement in self-esteem and quality of life.⁴¹

For the use of ozone as a therapy, according to the Madrid Declaration, it is necessary to consider three basic principles, namely: no harm, dose escalation, and application of the necessary concentration. The literature shows that the number of patients benefiting from ozone has increased in different parts of the world since the approval of the first edition of the declaration in 2010, although there is still resistance in the medical community, as well as the recognition of ozone in the legal field.⁴² Used for centuries and with benefits proven by several studies, ozone does indeed have excellent medicinal properties.

3) Limitations of ozone therapy use

When considering the use of ozone as an alternative method, it is necessary to take into consideration the limitations that it presents because this can interfere with the choice of its use. The publications in this review highlighted the toxic effects on the respiratory tract as an obstacle.^{20,25} Other side effects have been pointed out in the literature, including coughing, nausea, vomiting, and headache in case of contact with the mouth, nose, or eyes.⁴³

Ozone should never be inhaled, as it can cause undesirable effects because small amounts of ozone can irritate the throat and lungs, causing coughing, shortness of breath, and even respiratory complications if the exposure is severe.^{44,45} It is important to point out that the side effects of ozone therapy can vary according to the type of treatment applied.

No side effects were reported in the studies selected for this review, except for one publication that dealt with the consequences of ozone treatment for diabetic feet. The patient submitted to treatment used ozone therapy at first, but her condition worsened, which led to the amputation of one of her lower limbs.⁴³ In this case, the unfavorable outcome cannot be attributed to ozone therapy since the authors themselves stated that the clinical investigation of the patient, the use of ozone therapy, and the underestimation of the lesion were inadequate.

Ozone therapy has been shown to be safe and effective; however, it should be done carefully, according to the clinical condition of the patient, respecting the dose.

Before indicating ozone therapy, qualified professionals should know the entire patient's history and then indicate its use.⁴⁴

After the Ordinance No. 702 publication, on March 21, 2018, in which new practices were included in the Brazilian Política Nacional de Práticas Integrativas e Complementares (PNPICS), ozone therapy being one of these practices, the class councils sought to understand and regulate ozone therapy in the scope of practice of each profession.¹⁴

In Brazil, recently, with the publication of Normative Opinion 001, of 2020, by the Cofen, there was the recognition of ozone therapy as a complementary therapy to be performed by trained nurses, supporting the performance of this professional in the application of the therapy.¹⁵ The Brazilian Federal Council of Medicine was the only one that was against it and is still waiting for more scientific evidence, authorizing only experimental activities, although it is regulated in more than 50 countries. This position occurred after the analysis of scientific studies on the subject. The council claims that the studies do not provide doctors and patients with efficacy and safety, only allowing ozone therapy use as an experimental procedure.⁴⁶

The results of the use of ozone for diabetic foot ulcers are encouraging since studies have shown that ozone therapy has been an excellent complementary therapeutic tool that helps improve the quality of life of patients.^{9,47} In view of the above, it is necessary to clarify that all treatments have risks and contraindications, and ozone therapy is no different. Based on the studies analyzed, its use has been shown to be safe as long as all the guidelines for its use are followed.⁴⁸

The nurse has a fundamental role in the recovery of the patient, acting in all spheres of care, seeking improvement, and promoting actions in order to improve the conditions for the treatment of diabetic foot. Thus, the role of nursing in the use of ozone therapy as a complementary therapy for the treatment of lesions is growing.¹²

The study still has limitations because of the small number of publications of more robust articles, such as randomized studies, that present scientific evidence proving the effectiveness of the therapy.

Final Considerations

Through discursive analysis of the selected articles, it was identified that ozone therapy is effective and safe in the treatment of diabetic foot lesions. It is easy to apply, less invasive, speeds up the recovery period, and reduces the number of amputations.

However, it is evident that due to the small number of publications found, new research on this subject should be developed. Some studies describe the efficacy of ozone therapy as a complementary therapy; however, the lack of robust scientific evidence, such as randomized clinical trials, does not demonstrate the total effectiveness of ozone therapy as the procedure of choice for diabetic foot ulcers treatment.

It is hoped that the results of this study become a tool of incentive for the development of other research on the benefits of ozone therapy for the treatment of diabetic foot ulcers, especially by nurses, so that decision-making may be based on scientific knowledge in order to propose safer interventions in health care.

Contributions of the authors

Santos GS participated in the conception, design, search, and statistical analysis of research data, interpretation of results, writing and revision of the scientific article. Chaves JN participated in the conception, design, structuring of the introduction and methodology, and formatting of the scientific article. Miranda TCF participated in the conception, design, search, and statistical analysis of the research data and interpretation of the results of the scientific article. Azevedo RF participated in the orientation of all stages of the construction of the scientific article.

Conflicting interests

No financial, legal, or political conflicts involving third parties (government, private companies and foundations, etc.) have been declared for any aspect of the submitted work (including but not limited to grants and funding, advisory board participation, study design, manuscript preparation, statistical analysis, etc.).

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