ESTIMA
Brazilian Journal of Enterostomal Therapy

REVIEW ARTICLE
https://doi.org/10.30886/estima.v19.1090_IN

BENEFITS OF OZONE THERAPY IN THE TREATMENT OF FOOT ULCERS IN PEOPLE WITH DIABETES MELLITUS

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ABSTRACT

Objective: To identify the benefits of ozone therapy in the treatment of foot ulcers in people with diabetes mellitus. **Method:** Literature review carried out in the CINAHL, Cochrane Library, LILACS, PUBMED, SciELO, SCOPUS and Web of Science databases in the period between April and May 2020. In each database, the controlled descriptors were delimited in the Science Descriptors of Health and Medical Subject Headings, keywords defined: Ozone (Ozone), Diabetic Foot (Diabetic foot), with the help of the Boolean operator AND. **Results:** 14 primary studies were selected. Most studies have level II evidence, published in English, in different journals, from different parts of the world. 15 benefits of ozone therapy for the treatment of foot ulcers were identified, with a predominance of increased granulation tissue and intensification in the progress of tissue repair. **Conclusion:** The use of ozone therapy has shown several benefits in the progress in tissue repair of foot ulcers in people with diabetes, increased granulation tissue, promoted antiseptic and bactericidal activities, preventing oxidative stress.

DESCRIPTORS: Ozone. Diabetic foot. Therapeutics. Stomatherapy.

BENEFÍCIOS DA OZONIOTERAPIA NO TRATAMENTO DE ÚLCERAS NOS PÉS EM PESSOAS COM DIABETES *MELLITUS*

RESUMO

Objetivo: Identificar os benefícios da ozonioterapia no tratamento de úlceras nos pés de pessoas com diabetes *mellitus*. **Métodos:** Revisão de literatura realizada nas bases de dados CINAHL, *Cochrane Library*, LILACS, PUBMED, SciELO, SCOPUS e *Web of Science*, no período de abril a maio de 2020. Em cada base de dados, os descritores controlados foram delimitados nos Descritores em Ciências da Saúde e *Medical Subject Headings*, definidas as palavras-chaves: Ozônio (*Ozone*) e Pé Diabético (*Diabetic foot*), com auxílio do operador booleano AND. **Resultados:** Houve a seleção de 14 estudos primários. A maioria dos estudos possui nível II de evidência, publicados em inglês, em distintos periódicos, oriundos de diversas partes do mundo. Foram identificados 15 benefícios da ozonioterapia para o tratamento de úlceras nos pés, com predomínio de aumento do tecido de granulação e intensificação no progresso do reparo tecidual. **Conclusão:** O uso da ozonioterapia apresentou diversos benefícios no progresso do reparo tecidual de úlceras nos pés em pessoas com diabetes, aumentando o tecido de granulação, promovendo atividades antissépticas e bactericidas e prevenindo o estresse oxidativo.

DESCRITORES: Ozônio. Pé diabético. Terapêutica. Estomaterapia.

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Section Editor: Manuela de Mendonça F Coelho
Received: Apr. 2021, 25 | Accepted: Jun. 2021, 11
How to cite: Batista FWS; Araújo TM; Brandão MGSA; Ponte VA. Benefits of ozone therapy in the treatment of foot ulcers in people with diabetes mellitus. ESTIMA, Braz. J. Enterostomal Ther., 2021, 19: e1821. https://doi.org/10.30886/estima.v19.1090_IN

BENEFICIOS DE LA OZONOTERAPIA EM EL TRATAMENTO DE LAS ÚLCERAS DEL PIE EN PERSONAS COM DIABETES MELLITUS

RESUMEN

Objetivo: Identificar los beneficios de la ozonoterapia en le tratamiento de las úlceras del pie em personas con diabetes mellitus. **Método:** Revisión de la literature realizada en las bases de datos CINAHL, Cochrane Library, LILACS, PUBMED, SciELO, SCOPUS y Web of Science en le período de abril a mayo de 2020. En cada base de datos los descriptors controlados se delimitaron en los Descriptores de Ciencias Salud y Medicina. Encabezados de material, palabras claves definidas: ozono (ozono), pie diabético (pie diabético), con la ayuda del operador booleano AND. **Resultados:** Hubo una selección de 14 estudios primarios. La mayoría de los estudios tienen evidencia de nivel II, publicada en inglés, en diferentes revistas, de diferentes partes del mundo. Se identificaron 15 beneficios de la ozonoterapia para el tratamiento de las úlceras del pie, con predominio del aumento del tejido de granulación e intensificación en el avance de la reparación tisular. **Conclusión:** El uso de la ozonoterapia present varios beneficios en el avance en la reparación tisular de las úlceras del en personas con diabetes, aumento del tejido de granulación, promovió actividades antisépticas y bactecidas, previniendo el estrés oxidative.

DESCRIPTORES: Ozono. Pie diabético. Terapia. Estomaterapia.

INTRODUCTION

Ozone therapy is a therapeutic resource that uses the ozone molecule as its main component, and its application can be combined with oxygen in different concentrations. Manipulated since World War II, ozone has been touted as an adjuvant therapy for wound care[1].

This therapy is regulated by health surveillance agencies in several countries, such as Germany, China, Cuba, Spain, Greece, Portugal, Russia and Turkey[2]. In Brazil, ozone therapy is regulated by a Bill of the Federal Senate (227/2017), which authorizes the prescription of ozone therapy as a complementary treatment within the Unified Health System (*Sistema Único de Saúde-SUS*[3]).

The Federal Council of Nursing (*Conselho Federal de Enfermagem-COFEN*),through Normative Opinion No. 001 of 2020, it recognized and regularized ozone therapy as a complementary practice that can be carried out by nurses, under the condition that they are qualified. The agency guides professionals to reach 120 hours in courses on the subject. In nursing, technology can be applied to improve outcomes to treat injuries of different etiologies, thus raising the quality of care for patients affected with skin lesions[4].

A class of injury that can be treated with this type of adjuvant therapy is foot ulcers in people with diabetes mellitus (DM), which can involve several sensory, motor and foot deformities, which can aggravate and condition necrosis and/or serious infections, the result of incorrect and deficient actions in the prevention of this clinical condition[5].

Foot ulcers are the main cause of hospital admissions within the group of people affected with DM, therefore, it is the disease that promotes higher costs to health services, and the risk of non-traumatic amputations and even death[6]. The estimated number of deaths from diabetes and its complications in 2019 is 4.2 million people. Scary index that expresses the equivalence of one death every 8 seconds[7].

Thus, the treatment of foot ulcers in people with DM can benefit from the adjuvant action of ozone therapy, since the technology has oxidizing and disinfecting properties1. Clinical studies carried out in Iran and Russia identified a reduction in infection and amputations in the feet of people with DM who underwent treatment with ozone[8,9].

Knowing the benefits of new technologies and improving existing protocols can contribute to reducing the rates of amputations caused by DM complications, with the diabetic foot being one of the most relevant causes. Ozone therapy as an adjunct technology is an important milestone for health. Knowing its benefits and the best way to apply it to foot ulcers is essential. This generates optimization in the handling of technology, better quality assistance and significantly important

advances for the scientific field, arousing curiosity and epistemological considerations to be investigated by the scientific community. This study aims to identify the benefits of ozone therapy in the treatment of foot ulcers in people with DM.

METHOD

Type of study

This is a Literature Integrative Review (IR). In this type of study, a methodological approach is used, in which it is intended to carry out a review to fully understand the phenomenon examined. A combination of data from the literature and other deliberations is carried out, such as: definition, review of theories and analysis of questions about problems of peculiar models[10]. The textual corpus was built through scientific productions that report benefits of the application of ozone therapy in the treatment of diabetic foot ulcers.

Methodological framework

The integrative review followed six steps: I) Construction of the research problem; II) Sample screening from descriptors; III) Collection of relevant information; IV) Analysis of information related to the researched topic; V) Appreciation and interpretation of the collected results; and VI) Data exposure[11].

Methodological path

In this process, the PICO strategy was used: where P refers to the population, patient or problem (people with diabetic foot ulcers), I intervention (treatment with ozone therapy), element O refers to the outcome (beneficial effects of ozone therapy in the treatment of the lesion of interest in this study), whereas element C, of comparison between intervention or group, was not used due to the type of review[12]. Therefore, the guiding question of this study, based on the PICO method, is: "What are the benefits of ozone therapy in the treatment of diabetic foot ulcers?".

Data extraction source

The bibliographic survey took place between April and May 2020. To search for primary studies, seven databases were consulted: CINAHL (EBSCO), Cochrane Library (COCHRANE), *Literatura Latino-americana e do Caribe em Ciências da Saúde* (LILACS), National Library Of Medicine (PUBMED), Scientific Electronic Library Online (SciELO), Sciverse Scopus (SCOPUS), Web of Science, directly on their search engines or through the CAPES Periodical Portal. In each database, the controlled descriptors were delimited in the *Descritores em Ciências da Saúde* (DESC) and Medical Subject Headings (MESH), and defined the keywords: *Ozônio* (Ozone) and *Pé Diabético* (Diabetic foot). For the LILACS and SciELO databases, the search strategy used was "Ozônio AND Pé diabético". In the CINAHL, COCHRANE, PUBMED, SCOPUS and Web of Science databases, the strategy used was "Ozone AND Diabetic foot".

Data collection

There was no delimitation in the dates of publication of the studies, which followed in a timeless search. The delimited eligibility criteria were primary studies, which addressed therapeutic procedures in the treatment of diabetic foot ulcers with ozone therapy, available free of charge in full and published in Spanish, English and Portuguese. Publications that did not meet the guiding question of the study, studies with lesions of other etiologies, review articles, studies with animal species or *in vitro*, repeated theses, dissertations, letters to the editor or articles unavailable in the databases were excluded.

The extraction of data from primary studies was performed with the subsidy of an instrument developed and submitted to face and content validation[13].

The level of evidence was defined according to the classification: level I – meta-analysis of controlled and randomized studies; level II – experimental study; level III – quasi-experimental study; level IV – descriptive/non-experimental study or with a qualitative approach; level V – case report or experience; level VI - consensus and expert opinions[14].

Data analysis of the integrative review was elaborated descriptively. Each study included was analyzed in detail by the authors and two summary tables were prepared, containing the following information: the first table contains the title of the articles, source database, author citation, year and country of production, purpose of the study, sample, type of study and level of study; in the second, the organization is done by name of author(s), year of publication, frequency of application of ozone therapy, form of application and main result found by the research.

Ethical aspects

All scientific productions used in the research were duly cited and referenced, respecting copyright.

RESULTS

The initial search identified 210 records in the selected databases. After reading the title and abstract, 168 articles that did not meet the eligibility criteria were excluded, as they presented a different theme.

42 articles were selected for reading the title and abstract. There were 14 articles excluded due to duplication and, thus, 28 articles were selected for full reading. Among the 28 studies evaluated as fully eligible, 12 were incomplete and/or inaccessible, 1 article was carried out with an animal model and another was inconsistent with the study's guiding question, which were excluded. Thus, 14 primary studies comprised the sample of this IR, according to the flowchart described in Fig. 1.

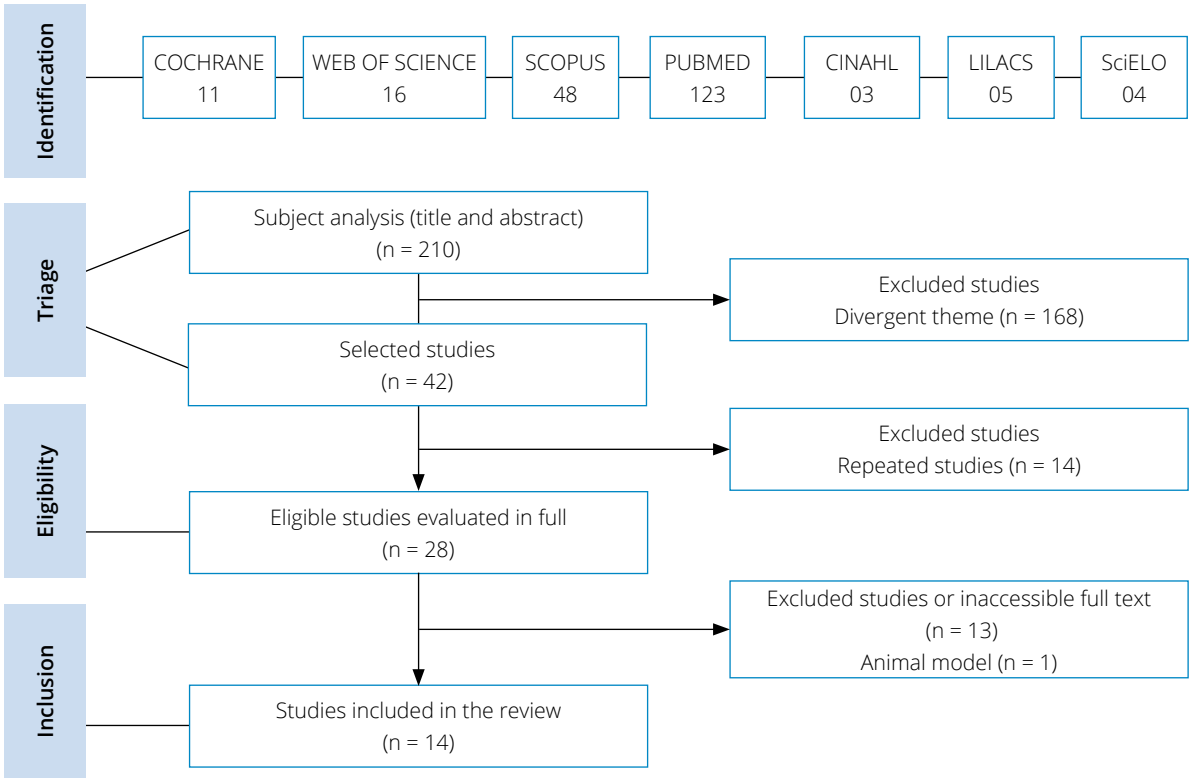

Figure 1. Flowchart of the selection of studies according to PRISMA. Redenção (CE) – 2021.

The final analysis included 14 studies with 1,148 people with diabetic foot ulcers, which aimed to identify the safety and/or efficacy of ozone therapy in the treatment of foot ulcers. Most studies have level II evidence, published in English (n = 9) in different journals, from different parts of the world, which are described in Table 1.

Table 1. Characterization of the studies included in the review. Redenção (CE) – 2021.

Nº	Title (Data base)	Authors (Year)/ Country	Objective	Sample	Type of Study/LE
1	Comprehensive treatment of diabetic hallux gangrene with lower extremity vascular disease: A case report (WEB OF SCIENCE)	Gao et al., 2019[15]/China	To describe the case of a diabetic patient with gangrene of the hallux and vascular disease of the lower limbs, treated with surgical debridement, ozone therapy and vascular interventional surgery.	01 patient	Case study/ V
2	Efficacy of comprehensive ozone therapy in diabetic foot ulcer healing (COCHRANE LIBRARY)	Izadi et al., 2019[8]/Iran	Identification of the safety and efficacy of ozone in healing foot ulcers in patients with diabetes.	200 patients	Randomized clinical trial/ II
3	Evolución de las úlceras de pie diabético con el tratamiento mixto de Heberprot-P® y ozonoterapia (LILACS)	Martínez et al., 2019[16]/Cuba	Determining the evolution of diabetic foot ulcers with Heberprot-P® mixed treatment and ozone therapy.	323 patients	Retrospective and descriptive study/ IV
4	Ozone Therapy in the Comprehensive Treatment of Diabetic Foot Syndrome (SCOPUS)	Teuvov et al., 2017[9]/Russia	Evaluate the effectiveness of the application of ozonized solutions in the complex treatment of diabetic foot syndrome.	37 patients	Randomized clinical trial/ II
5	Ozone therapy effectiveness in patients with ulcerous lesions due to diabetes mellitus (SCOPUS)	Rosul; Patskan, 2016[17]/ Ukraine	Study the effectiveness of ozone use in complex therapy in patients with diabetic foot.	47 patients	Randomized clinical trial/ II
6	Atención multidisciplinaria con terapia avanzada y de recurso a pacientes con pie diabético en Mayabeque (LILACS)	Barrios et al., 2015[18]/Cuba	Describe the model of care for patients with diabetic foot used in the consultation.	113 patients	Retrospective and descriptive study/ IV
7	Beneficios de la intervención con ozonoterapia em pacientes con pie diabético neuroinfeccioso (SciELO)	Duarte et al., 2014[19]/Cuba	Evaluate the benefits of ozone intervention in type 2 diabetic patients suffering from neuroinfectious diabetic foot.	150 patients	Randomized clinical trial/ II
8	Increased Growth Factors Play a Role in Wound Healing Promoted by Noninvasive Oxygen-Ozone Therapy in Diabetic Patients with Foot Ulcers (WEB OF SCIENCE)	Zhang et al., 2014[20]/China	Evaluate the effects of ozone therapy on healing and expression of VEGF, TGF- and PDGF in early stage wounds after treatment.	50 patients	Randomized clinical trial/ II
9	Ozone Therapy in Diabetic Foot and Chronic, Nonhealing Wounds (SCOPUS)	Fathi; Mawsoufn; Viebahn-hänsler 2012[21]/Egypt	To study the effectiveness of using ozone in complex therapy in patients with diabetic foot.	63 patients	Case series/ V

continue...

Table 1. Continuation...

Nº	Title (Data base)	Authors (Year)/ Country	Objective	Sample	Type of Study/LE
10	Efficacy of Ozone-Oxygen Therapy for the Treatment of Diabetic Foot Ulcers (WEB OF SCIENCE)	Wainstein et al., 2011[22]/ Israel	To examine the effectiveness of non-invasive ozone and oxygen therapy in the treatment of diabetic foot ulcers.	61 patients	Randomized clinical trial/ II
11	*Ozonoterapia como tratamento adjuvante na ferida de pé diabético (LILACS)*	Cardoso, et al., 2010[23]/Brazil	To report the treatment of a diabetic patient, atherosclerotic, with a history of infected ulcer associated with osteomyelitis in the fourth right toe, with blood perfusion, incompatible with healing.	1 patient	Case study/ V
12	Major Ozonated Autohemotherapy in Chronic Limb Ischemia with Ulcerations (SCOPUS)	Monte; Der-Zee; Bocci 2005[24]/ Netherlands	Report the beneficial effects of autohemotherapy with ozone in two patients affected by painful and untreatable leg ulcers.	2 patients	Case study/ V
13	Therapeutic efficacy of ozone in patients with diabetic foot (COCHRANE LIBRARY)	Martínez-Sánchez et al., 2005[25]/Cuba	Evaluate the effectiveness of ozone in the treatment of patients with type 2 diabetes, suffering from complications in diabetic feet and its effects on oxidative stress, hyperglycemia and some markers of endothelial damage, to compare ozone with antibiotic therapy.	100 patients	Randomized clinical trial/ II
14	Efecto del ozono sobre la activación plaquetaria en pacientes diabéticos tratados con ozonioterapia: informe preliminar (SCOPUS)	Batista et al., 2001[26]/Cuba	Check whether or not there was inhibition of platelet aggregation in people with ischemic or neuroinfective diabetic foot after treatment with ozone.	9 patients	Case study/ V

LE = Level of evidence; VEGF = vascular endothelial growth factor; TGF-β = transforming growth factor beta; PDGF = platelet-derived growth factor.

Table 2 shows the application protocols for ozone therapy and the results achieved with the use of this therapy. The application frequency varied according to the assessment of the lesion; the application time ranged from two weeks to months. Different methods of application of ozone therapy were used, such as local application, intravenous, rectal insufflation and intralesional injection, in different concentrations of ozone.

The most used method was the local application, through bagging of ozone in the lesion. Only in the intralesional injection method were there negative results. In other studies, there was an improvement in the tissue repair process, granulation, epithelialization, pain reduction, antisepsis, reduction in the need for major and minor amputations, improvement in blood glucose levels, in addition to bactericidal and fungicidal effects.

Table 3 shows the 16 benefits of ozone therapy reported in the studies analyzed. The most frequent benefits were progress in tissue repair and granulation, antiseptic and bactericidal effects, prevention or inhibition of oxidative stress, and improvement in vascularization and glycemic control.

Table 2. Frequency distribution, form of application and main result of the studies. Redenção (CE) − 2021.

Authors and year of publication	Application frequency	Form of application	Main result
Gao et al., 2019[15]/China	Application of ozone daily, during the dressing.	Local application of a pouch filled with concentrated ozone, positioned on the foot, for 20 minutes. The patient started with an ozone concentration of 30μg/mL. After two consecutive treatments the ozone concentration gradually increased by 5μg/mL.	Improves granulation tissue growth and maintains a relatively clean wound environment.
Izadi et al., 20198/Iran	Ozone application twice a week (interval of at least 24 h) until wound closure.	Local treatment using special bags with ozone, for 30 minutes. Ozonized gel (Ozolive) was applied to the wounds every 12 hours and then dressed with sterile gauze. Subcutaneous injection of ozone-oxygen was performed around the wound. In systemic use, patients received a mixture of ozone and oxygen, via rectal or intravenous administration.	Cure and reduction of infections and amputations, which has been shown to be effective in ozone therapy in curing diabetes ulcers and reducing infections and amputations.
Martínez et al., 2019[16]/ Cuba	Daily application, from Monday to Friday, once a day (in the morning), for two weeks.	Local treatment, by placing the affected limb in a plastic bag, sealed with plaster and filled with an ozone/oxygen mixture at an ozone concentration between 50 and 60 mg.	Improved wound healing and decreased number of minor amputations.
Teuvov et al., 2017[9]/Russia	Daily application. The duration of treatment varied according to the patients' general conditions.	Application of local and general ozone sessions. For general ozone therapy, 200 mL of 0.9% saturated ozone solution of sodium chloride was injected intravenously, with an ozone concentration of 800-1000 mcg/L. Local ozone therapy included daily wound dressings and the introduction of ozonized saline solution with concentrations of 3-4 mg/L.	Improvement in the general condition of patients, decrease in endotoxicosis rates, acceleration of regenerative processes in purulent wounds, decrease in the number of microbial bodies in spots, reduction in bed days.
Rosul; Patskan, 2016[17]/ Ukraine	Daily application for 12 to 14 days.	Application of 200 mL of ozonized physiological saline solution at an ozone concentration of 1000 to 1300 mcg/L intravenously. For local therapy, ozone dissolved in 0.9% NaCl and ozonized sea buckthorn oil at a concentration of 4000 mcg/L were used.	There was an improvement in the healing process, improvement in lipid peroxidation and antioxidant protection indices, with a reduction in hospital stay and treatment of the diabetic foot.
Barrios et al., 2015[18]/Cuba	Application of 12 sessions, with unknown interval.	Local application with plastic bags (concentration of 40-50 mgL^{-1} of O^3 volume) and systemic application by rectal insufflation (150 mL at a concentration of 30-40 mgL^{-1}).	Lesions fully healed, improves the healing process with bactericidal and fungicidal effects of ozone.
Duarte et al., 2014[19]/Cuba	Application for 21 days, with omitted interval.	Local application with plastic bags (concentration of 40-50 mgL^{-1} of O^3 volume depending on foot size) until filling, and systemically by rectal insufflation.	Improved healing rate and aseptic state, with re-epithelializing edges and granulation tissue; the wounds were fully healed and there were no major amputations.
Zhang et al., 2014[20]/China	Application of ozone for 30 minutes for 20 days.	Topical oxygen and ozone therapy with 52 μg/mL of ozone (total volume: 20–50 mL) in a special pouch for 30 minutes, using an ozone generating device (Humazon Promedic, German), in addition to the standard treatment.	Improves healing rate and VEGF, TGF-β and PDGF.

continue...

Table 2. Continuation...

Authors and year of publication	Application frequency	Form of application	Main result
Fathi; Mawsoufn; Viebahn-hänsler 2012[21]/Egypt	Varied applications until reaching maximum benefit in the treatment process.	Rectal insufflation and application of topical ozonized solutions (in one case, ozonized water compresses were used and in another ozonized oil, in addition to application).	Improvement in healing, size of the area with granulation tissue and tissue vascularization. Improvement in glycemic control, in addition to reports of improvement in heart condition.
Wainstein et al., 2011[22]/ Israel	The treatment was divided into two phases: 1st – Application 4 times a week for a maximum of 4 weeks or until granulation of 50% of the wound. The break did not exceed 1 day 5 days a week. 2nd - Application twice in 1 week to complete the 12 weeks of treatment.	Local ozone therapy through hermetic sealing and ozone/oxygen gas mixture introduced into the sealing system.	Significant improvement in tissue repair of the diabetic foot compared to conventional treatment, especially when protocols for foot ulcers with a surface < 5 centimeters are administered.
Cardoso, et al., 2010[23]/ Brazil	Application for 14 weeks. Does not report application interval and frequency.	Topical therapy through baths (hydro-ozonotherapy- Ozonomatic®), followed by dressings with ozonized oil. In the 10th week of treatment, a gaseous mixture (bagging) of oxygen and ozone was introduced, before hydro-ozone therapy.	The treatment promoted antiseptic properties, which improved local oxygenation due to induced neovascularization and accelerated tissue repair.
Monte; Der-Zee; Bocci 2005[24]/ Netherlands	Application twice a week at intervals of two to three days, for several months.	Self-hemotherapeutic: gaseous mixture composed of medicinal oxygen (96%) and ozone (4%). The oxygenated ozone associated with the blood was reinfused into the donor for 20 minutes.	Improvement of pain, swelling, healing and promotion of a sense of well-being. Autohemotherapy resulted in complete healing of difficult-to-heal ulcers.
Martínez-Sánchez et al., 2005[25]/ Cuba	Application of 20 sessions. It does not report the intervals adopted for the application of each therapy.	Rectal administration (10 mg ozone dose, ozone concentration: 50 mg/L). In local therapy, the lesion was covered with a plastic bag, sealed in the leg, under vacuum with ozone at a concentration of 60 mg/L for 1 hour. For topical therapy, ozonized sunflower oil was used.	Ozone treatment improved glycemic control, prevented oxidative stress, and levels of organic peroxides and activated superoxide dismutase were normalized.
Batista et al., 2001[26]/Cuba	Daily application for 10 to 20 days.	Rectal administration of 200 mL of ozone at a concentration of 50 to 80 mg/L for 1 to 2 min, combined, in some cases, with local application of plastic bags with ozone at a concentration of 80 mg/L, for a maximum period of 2 hours.	There was a reduction in the percentage of platelet aggregation at the end of ozone therapy compared to initial values.

VEGF = vascular endothelial growth factor; TGF-β = transforming growth factor beta; PDGF = platelet-derived growth factor.

Table 3. Benefits of using ozone therapy in the treatment of diabetic foot. Redenção (CE) – 2021.

Benefits of using ozone therapy	Articles
Accelerates tissue repair and increases granulation tissue	1; 2; 3; 4; 5; 6; 7; 8; 10; 11; 12; 13; 14
Antiseptic and bactericidal properties	1; 2; 3; 4; 6; 7; 10; 11; 12
Prevents or inhibits oxidative stress	2; 4; 5; 7; 8; 12; 13; 14
Improves tissue vascularization	1; 5; 7; 10; 11; 12; 13
Improves glycemic control	4; 5; 6; 8; 10; 14
Decreases amputation rates	2; 3; 7; 10; 12
Improves the pain	4; 5; 7; 11; 13
Reduces hospital stay	3; 5; 7; 14
Indicates systemic improvement beyond the injury	2; 4; 5; 10
Causes a feeling of well-being	5; 10; 13
Reduces edema	4; 5; 13
Reduces bed time	4; 5
Multiplies collagen fibers	8
Increases the expression of VEGF, TGF-β and PDGF proteins.	8
Reduces the percentage of platelet aggregation	15

VEGF = vascular endothelial growth factor; TGF-β = transforming growth factor beta; PDGF = platelet-derived growth factor.

DISCUSSION

The analysis of the results of the studies included in the review allowed the identification of compliance regarding the use of ozone therapy as an adjuvant for the treatment of foot ulcers in people with DM.

Ozone therapy proved to be a beneficial therapy, with a predominant outcome of increased granulation tissue and advances in the tissue repair process. Furthermore, studies suggest that ozone therapy has antiseptic and bactericidal properties, acts to prevent or inhibit oxidative stress, improves the level of pain, tissue vascularization and glycemic control. Cuban studies report that such characteristics can significantly contribute to the reduction of hospital admissions[16,19,25].

Ozone therapy also showed signs of systemic improvement and promoted physiological benefits in the user's body as a whole. A study in Iran identified as a benefit of ozone therapy the reduction in sedimentation of erythrocytes, c-reactive protein and reduced fasting blood glucose[8].This data demonstrates that the therapy under study can provide the patient with secondary outcomes that help in conducting foot ulcer healing.

Studies in Russia, Ukraine and Egypt corroborate the beneficial results of the use of ozone not only for ulcers, since this therapy secondarily induces the normalization of the white blood cell count, with a reduction in segmented leukocytes, an increase in the number of lymphocytes and monocytes, and characteristic of immunomodulation, which is documented as a transition from degenerative to regenerative inflammatory effect[9,17,21].

Systemic ozone therapy also reduced reports of complaints of thirst, dry mouth sensation, polyuria, and increased catalase activity, in addition, there is a record of clinical cardiac improvement[17,21]. Generating observational data with a larger group of patients and adopting a research model with controlled clinical trials may extend the confidence interval and reveal other benefits or reactions not yet known. Clinical studies in Israel and Iran showed that the study group that used ozone therapy had a significantly higher rate in the proportion of complete wound closure[8,22]. Israeli researchers infer mean wound healing time of ±36.05 and ±69.44 days, with an interval of 15 to 180 days in the ozone group, while in the control group the mean time was greater than 180 days[8]. A study in Brazil, which evaluated the

progress of conventional wound treatment in people with DM, identified that the median for healing time was 248 days (IQ = 125-492)[27]. These data demonstrate the effectiveness of ozone use in tissue repair time.

There was a predominance of local application of ozone, with ozone in bags (bagging). The use of ozone in this way was successfully used by researchers from China, Israel and Cuba, through an occluded chamber, with a mixture of oxygen and ozone[15,16,20,22]. The greatest preference for local application in bagging may lie in the fact that it requires simple, low-cost, safe and minimally invasive techniques, and, thus, it is more acceptable to patients.

However, there is variability in application frequency, formulation type and ozone/oxygen concentration. This reason can be related to the fact that there is a variability of protocols, but none has been disseminated as the most suitable for use in diabetic foot. Another point that can explain this situation is the fact that ozone therapy is considered a contemporary technology, which can generate the existence of a variability of tests and studies that are still in progress.

The safety of handling ozone therapy and its effects is a factor that has stimulated research in the area. A comprehensive use of options, technological innovations and the absence of side effects provide scientists with significant margins of safety. *A priori*, it is revealed that O^3 it has no toxicological effects or influence on the structure of deoxyribonucleic acid (DNA), and no adverse reactions have been reported by clinical trials, it seems that there is no risk to patient safety[8,18,20].

Highlighting the beneficial effects of ozone therapy may help nursing professionals to develop advanced practices for the treatment of foot ulcer injuries in people with DM. In Brazil, COFEN, through Resolution number 567, of January 29, 2018, declares that the treatment of wounds and their assessment are the responsibility of the nurse, as well as the elaboration of protocols, selection and indication of new technologies for treatment of the condition[28].

Knowing innovative adjuvant techniques is an evolutionary milestone for each field, investigating and elaborating questions is also a function that brings implementation of care, each process that generates research, produces science and entails several welcome conditions in the user's life. Despite having limitations, such as the unavailability of some studies in their entirety, this review presents promising data regarding the benefits of using ozone therapy in the treatment of foot ulcers in people with DM. The data found in this review may contribute to evidence-based practice, innovation in nursing care for people with DM and foot ulcers.

New studies are expected to show increasingly promising results on the use of ozone in the treatment of diabetic foot, frequency of application, type of formulation and ozone/oxygen concentration to validate the efficacy and safety data demonstrated in this review.

CONCLUSION

The use of ozone therapy in the treatment of diabetic foot has the benefit of progress in tissue repair, increase in granulation tissue, antiseptic and bactericidal properties, prevention or inhibition of oxidative stress, improvement in tissue vascularization, improvement in glycemic control, improvement in pain , decreased amputation rates, reduced hospital stay, reduced edema, multiplication of collagen fibers, reduced percentage of platelet aggregation and increased expression of vascular endothelial growth factor (VEGF) proteins, transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF). It is noteworthy that ozone therapy points to an arsenal of therapeutic resources to accelerate the healing of foot ulcers in diabetic individuals and at a lower cost than conventional treatments.

AUTHORS' CONTRIBUTION

Conceptualization: Batista FWS, Araújo TM e Brandão MGSA; Methodology: Batista FWS, Araújo TM e Brandão MGSA; Investigation: Batista FWS e Brandão MGSA; Writing – First version: Batista FWS, Araújo TM e Brandão MGSA; Writing – Reviewing & Editing: Batista FWS, Araújo TM, Brandão MGSA, Ponte VA; Supervision: Araújo TM e Brandão MGSA.

DATA STATEMENT AVAILABILITY

Not applicable.

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