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*Research Article*

# Physical Treatment of Diabetic Foot Ulcers—Preliminary Study for Topical Application of Oxygen or Ozone Auxiliary Treatment of Diabetic Foot Ulcers

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Diabetes mellitus is one of the most common metabolic diseases in which one of the most serious complications is the diabetic foot ulcer (DFU). The aim of the study was to compare the efficacy of two physical therapeutic methods: topical oxygen therapy and topical ozone therapy in the treatment of DFU with the calculation of the financial costs for both applied physical methods. The study included 85 patients, 47 male (55.2%) and 38 female (44.7%) in age range between 40 and 90 years (mean age: 67.82 ± 12.42 years) with hard to heal diabetic foot ulcers. The mean diabetic foot ulcer duration was 3.6 ± 1.23 years. Patients were randomized into two study groups not significantly different in terms of age, body mass index (BMI) value, and baseline ulcer surface area value, who underwent topical oxygen therapy (group I) and topical ozone therapy (group II), respectively. Both the groups underwent a total of 30 daily treatments lasting 30 minutes, in 2 sessions of 15 treatments with a 14-day break between sessions. Progress in wound healing was evaluated by computerized planimetry and the pain intensity was assessed with use of a VAS scale. After the treatment, the ulcer area in group I decreased by an average of 33.25 ± 10.97% and by an average of 28.67 ± 14.47% in group II ($p = 0.030$). On the other hand, the intensity of pain ailments after the treatment was statistically significantly decreased in group I by an average of 57.13 ± 16.24% while in group II by an average of 40.21 ± 14.53% ($p < 0.001$). After application of topical oxygen therapy and topical ozone therapy in the treatment of diabetic foot ulcers a statistically significant reduction in the surface area of treated ulcers in objective planimetric assessment was observed, with local oxygen therapy showing only a slight advantage in this regard. Both compared methods also caused a statistically significant reduction in the pain intensity, while local oxygen therapy shows statistically significantly better analgesic effectiveness. Due to the calculated moderate cost, both applied methods appeared to be cost-effective.

## 1. Introduction

Chronic and difficult-to-heal wounds pose a serious challenge to healthcare systems around the world. Improperly treated, they can lead to very serious complications. The incidence of hard-to-heal wounds defined as wounds that fail to heal with standard therapy in an orderly and timely manner in the general population is 2.21 per 1,000 population members [1]. The high costs associated with medical care for hard-to-heal wounds make one of the important problems that limit the effectiveness of its treatment [1, 2].

One of the persistent, hard-to-heal wounds is diabetic foot ulcer (DFU), an important complication of diabetes. Progressive structural and metabolic lesions in the foot may lead to ulceration and/or destruction of deep tissues in combination with neurological disorders, leading to necrotic changes and limb amputation [3, 4]. The universal nature of

DFU is evidenced by its high frequency of occurrence. DFU develops in about 20% of diabetic patients [5]. In Poland, statistical data from 2017 indicated that the number of patients with DFU over 15 years of age was 2.2 million [6]. In order to decrease this incidence, it is extremely important to take preventive measures, educate patients and make patients aware of the need to react quickly in the event of alert symptoms [7, 8]. It should be remembered that in many cases the mere conduct of a personal (interview) and physical (physical examination), supported by appropriate laboratory tests, allows for the correct diagnosis [9]. The risk factors leading to the occurrence of DFU include, among others: obesity, stimulants (smoking and alcohol abuse), improper nutrition, and neglect in foot care [10, 11].

Along with the intensive development of medicine and related sciences, research is constantly being carried out on the possibility of using various methods in the treatment of difficult-to-heal wounds, including those using the healing effects of selected physical factors. These methods mentioned in the literature are inter alia, local ozone therapy, and local oxygen therapy [12].

Topical oxygen therapy (TOT) is a physical method involving the topical application of 100% oxygen or a mixture of gases with a high oxygen content at a pressure above one physical atmosphere (ATA) to diseased tissues. The beneficial therapeutic effect of topical oxygen therapy in the diabetic foot ulcer is mainly related to the analgesic, anti-inflammatory, and antiedema effects. The regenerative effect of TOT, related to the improvement of local blood flow and the supply of increased amounts of oxygen to ischemic and hypoxic tissues, resulting in faster wound healing, is also of great therapeutic importance [13, 14].

In turn, topical ozone therapy is a physical treatment involving the local application of ozone to pathologically changed tissues. Ozone ($O_3$) is an active form of oxygen used for therapeutic purposes, most often in the form of dry baths in an oxygen-ozone mixture in the proportion of 5% by volume of ozone and 95% by volume of oxygen. The recommended therapeutic ozone concentration is 50–120 $\mu$g ozone/ml oxygen. In ozone generators producing ozone from oxygen supplied from a cylinder, the ozone concentration at the device outlet ranges from 5 to 70 mg/l, and the maximum pressure is 0.06 MPa. One of the therapeutic mechanisms of topical ozone therapy, especially in patients with infected wounds, is bactericidal effect related to the destruction of bacterial cell membranes due to oxidation of nonsaturated fatty acids forming those membranes and enzymatic proteins in cytoplasm by active singlet oxygen (acting as a strong oxidant generated during dissociation of ozone molecule), resulting in disturbances of the activity of numerous cellular organelle, injury of DNA and in consequence in bacterial cell apoptosis [15, 16]. Regardless of its bactericidal effect, ozone also reduces the severity of inflammation in the area of ulcers by inhibiting the migration of mast cells, reduces the release of lysosomal enzymes and some acute phase proteins, and stimulates the formation of eosinophils and antioxidants, as well as activates the Krebs cycle in erythrocytes causing increase in the amount of oxygen and ATP released into the tissues. Thanks to these effects, tissue oxygenation and nutrient supply in tissues are increased. When properly applied topically, ozone is not harmful to the patients' organism [17, 18].

*1.1. Aim of the Study.* The aim of the study was to compare the effectiveness of local oxygen therapy and local ozone therapy in the treatment of diabetic foot ulcers with the calculation of the financial costs for both applied physical methods.

## 2. Materials and Methods

The study included 85 patients, 47 male (55.2%) and 38 female (44.7%), with diabetic foot ulcers (neuropathic-ischemic) hospitalized in the Department of Internal Medicine, Angiology and Physical Medicine in Bytom (Poland) in the period: 2019–2021, who were (by means of drawing lots) assigned to two research groups, respectively: group I consisting of 42 patients (20 women and 22 men) who underwent local oxygen therapy and group II consisting of 43 patients (18 women and 25 men) who underwent local ozone therapy. No patient had undergone revascularization before participation in the study.

The mean age of all treated patients was $67.82 \pm 12.42$ years, respectively: $69.09 \pm 11.35$ years in group I and $66.58 \pm 13.41$ years in group II, and the difference in age between groups I and II was not statistically significant ($p = 0.621$). The average BMI index was $25.47 \pm 2.26$ kg/m$^2$ in group I and $25.01 \pm 1.98$ kg/m$^2$ in group II, and the difference in BMI values between the groups was not statistically significant ($p = 0.603$). The mean duration of the DFU was $3.92 \pm 1.19$ years in group I and $3.27 \pm 1.2$ years in group II, respectively. Also in this case, the difference was not statistically significant ($p = 0.120$).

Inclusion criteria for the studies were as follows: patient consent to participate in the study, diagnosis of diabetic foot ulcers with ulcerations located in the area of one foot, age 40–90 years. Exclusion criteria were as follows: lack of patient consent to participate in the study, ulcer etiology other than diabetic foot ulcers, deep vein thrombosis, acute ischemia of the lower limbs, age <40 years and >90 years, generalized infection requiring systemic antibiotic therapy, and contraindications to the treatment with topical ozone therapy and topical oxygen therapy.

Before starting physical treatment, the mean values of the ulcer area in group I, $6.85 \pm 1.16$ cm$^2$, and in group II, $7.25 \pm 1.26$ cm$^2$, did not differ statistically significantly ($p = 0.128$). There were also no significant statistical differences in the intensity of pain experienced before the start of treatment between group I (mean value in the visual-analogue VAS scale = $7.88 \pm 0.73$ points) and group II (mean value in the VAS scale = $7.93 \pm 0.93$ points) ($p = 0.927$).

Before starting a cycle of ozone therapy and local oxygen therapy procedures if it was necessary to conduct surgical wound debridement, in order to remove necrotic tissues or purulent infiltration accompanying the ulcer.

Computer software for planimetric assessment of ulceration surface area was used for digital image processing [19]. In this method, on the image of the ulcer obtained from a digital camera, the researcher drew the perimeter and surface of the wound and then automatically closed the drawn contours, creating a closed curve that accurately reflects the shape and size of the ulcer. The program automatically calculated the ulcer surface area within the previously defined contour. Primary measurement results were obtained in pixels. After calibration, performing the scaling process and appropriate calculations the results are presented in square centimeters accurately describing the size of the ulceration area [19].

In addition, before the beginning and after the end of the therapeutic cycle the assessment of pain intensity with the use of a VAS scale was performed.

The study was conducted in accordance with Declaration of [20] and its protocol has been accepted by the local bioethical committee at Medical University of Silesia in Katowice, Poland (approval reference number: KNW/0022/KB1/102/II/16/19). Every patient enrolled to the study has signed written informed consent approval for all procedures conducted in the study.

## 3. Methodology of Physical Treatments

Local oxygen therapy in group I were performed using the OXYBARIA-S device (Fasser S. A., Tarnowskie Góry, Poland) [21]. The treated limb was placed in the treatment chamber, which was sealed with an elastic collar at the thigh level. The concentration of oxygen introduced into the chamber was about 95%, at a pressure of 1.5 ATA and a flow rate of about 5 L/min. The treatment cycle included 30 treatments performed once a day for 30 minutes in 2 series of 15 treatments (excluding Saturdays and Sundays). The interval between series was 4 weeks.

The Ato-3 device by Metrum Cryoflex (Blizne Łaszczyńskiego, Poland) was used for ozone therapy in patients from group II [22]. Ozone was applied to the surface of the ulcer in the form of an oxygen-ozone mixture (5% ozone and 95% oxygen) with a concentration of 40 $\mu$g/ml using the so-called "Ozone bag." The duration of a single procedure was 30 minutes. Treatments were also performed daily for 30 days in two series of 15 treatments (except Saturdays and Sundays). The interval between two series of ozone therapy treatments was 4 weeks in order to counteract the potential risk of exposing patients to the negative effects of long-term effects of ozone on the skin around the ulcer and deeper tissues. Considering that topical ozone therapy was applied to the wound with a plastic bag creating a tight closed space around the ulcer, it was practically impossible for the patient to inhale ozone, and thus, the harmful effects of ozone entering the body through the lungs.

During a cycle of physical procedures in both the groups of patients similar conventional pharmacological treatment was applied, in addition, it was applied to the wound Allevyn Adhesive Ag dressing (Smith & Nephew) in order to maintain proper humidity of the wound, and allowed for an antibacterial effect and improvement of wound cleanliness.

*3.1. Statistical Analysis.* Statistical analysis was performed with use a Statistica 13 package (Statsoft, Poland). The Shapiro–Wilk test was used to test the normality of data. There were non-normal distributions of data. The Mann–Whitney $U$ test and Wilcoxon test were used to compare two unmatched and matched group of nonparametric data, respectively. The level of statistical significance was $p < 0.05$.

## 4. Results

After the end of the therapeutic cycle, both study groups showed a statistically significant reduction in the ulcer area ($p < 0.001$), with the mean ulcer area in group I of $4.62 \pm 1.26\ \text{cm}^2$ being statistically significantly lower than the mean ulcer area in group I. In group II, it was $5.26 \pm 1.62\ \text{cm}^2$, and the obtained difference was at the border of statistical significance ($p = 0.051$) (Figure 1).

After the end the therapeutic cycle, both study groups showed a statistically significant reduction in the intensity of accompanying pain ($p < 0.001$), while the mean value of pain intensity assessed on the VAS scale, in group I of $3.4 \pm 1.36$ points, was statistically significantly lower compared to the group II, where it was $4.72 \pm 1.18$ points ($p < 0.001$) (Figure 2).

In group I, the percentage reduction in the area of ulcers after the applied treatment was on average $28.67 \pm 14.47\%$, while in group II it was $33.25 \pm 10.97\%$, and the difference was statistically significant ($p = 0.030$). In group I, the percentage reduction in the intensity of pain assessed using the VAS scale was on average $40.21 \pm 14.53\%$, while in group II it was on average $57.13 \pm 16.24\%$, and the difference was statistically significant ($p < 0.001$) (Table 1).

No patients had 100% ulcer healing. In group I, the reduction of the wound surface by 50% and more was noted in 4 patients (9.3%). In 39 patients (90.69%) the reduction of the wound surface was achieved by less than 50%. In group II, 3 patients (7.14%) achieved a reduction of the treated ulcer area by 50% or more. In 39 patients (92.85%), the ulcer area was reduced by less than 50%. In group I, the smallest improvement, the reduction of the ulcer surface area of 3.75%, was noted in 1 patient. On the other hand, in group II the smallest improvement, the reduction of the ulcer surface area by 12.5%, was also obtained in 1 patient. No patients in group I or group II had any enlargement of the ulcer surface after the end of the therapeutic cycle.

In group II, 2 patients (4.76%) had complete pain relief, but no such case was reported in group I. In 32 patients (76.19%) in group II, pain was reduced by 50% or more, while in group I, pain was reduced by 50% and more was found only in 13 (30.23%) treated patients. The smallest improvement in the intensity of perceived pain was 25% and it was obtained in 1 patient in group II. In group I, the smallest improvement was 22% and it was also noted in 1 patient. No increase in pain intensity was observed in any of the patients from both the groups after the end of the therapeutic cycle.

The results of treatment obtained in both the groups were also compared in terms of the duration of the disease. Among patients suffering for a shorter time (1–3 years), the

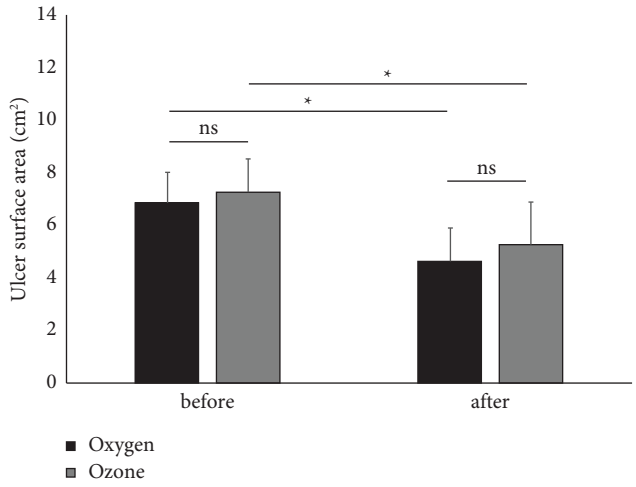


Figure 1: Comparison of the ulcer surface area before and after the treatment cycle in group I treated with local oxygen therapy and in group II treated with local ozone therapy. $p$ value <0.05 is represented as * and $p$ value >0.05 is indicated by "ns" for not significant.

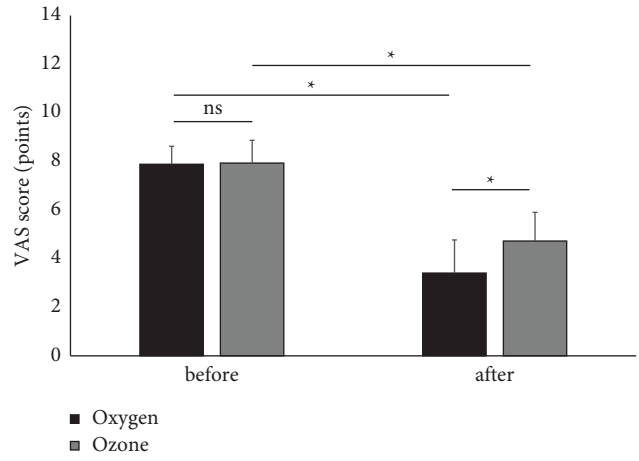


Figure 2: Comparison of the pain intensity symptoms before and after the end of therapy in group I treated with local oxygen therapy and in group II treated with local ozone therapy. $p$ value <0.05 is represented as * and $p$ value >0.05 is indicated by "ns" for not significant.

surface areas of treated ulcers before treatment was smaller in both group I and group II. The ulcers in this group were also accompanied by lower pain intensity.

After the treatment, in both the groups of patients, the ulcer surface area in the subgroup of patients with a shorter disease duration was statistically significantly lower compared to the subgroup of patients with a longer duration of the disease, while only in group II the difference in the percentage change in the ulcer area in both the subgroups was significant statistically ($p = 0.015$). Similarly, after the treatment, in both the groups of patients, the intensity of pain experienced in the subgroup of patients with a shorter duration of the disease was statistically significantly lower than in the subgroup of patients with a longer duration of the disease, while only in group I the difference in the percentage change in the pain intensity in both the subgroups was statistically significant ($p < 0.001$) (Table 2).

The total cost of the treatment including local hyperbaric oxygen therapy procedures (3,345 Euro), daily dressings with specialistic Ag dressing (9,810 Euro), and other dressing materials (3180 Euro) were ca. 16.335 Euro. On the other hand the total cost of the treatment including ozone therapy procedures (2,970 Euro), daily dressings with specialistic Ag dressing (9,162 Euro), and other dressing materials (2,228 Euro) were ca. 14.360 Euro. It can be concluded that the total costs of the treatment with the use of both physical methods were similar and relatively moderate.

## 5. Discussion

Along with the increase in the incidence of diabetes, patients and doctors more and more often struggle with one of its most important complications-diabetic foot syndrome [3, 12]. The two main causes of DFU are diabetic neuropathy and peripheral vascular disease (PVD) [5]. It is also the most common cause of hospitalization of patients with diabetes, among whom approximately 25% are at risk of developing DFU. Moreover, in 20% of patients DFU ends with limb amputation, and further treatment is a huge economic burden not only for the health care system but also for the patients themselves [4, 6, 23].

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the prevention and management of diabetic foot disease since 1999. The recommendation for sensible consideration of various alternative therapies, including topical oxygen therapy and ozone therapy, remains valid [12]. According to the latest standards for the treatment of DFU ulcers, the MOIST strategy should be followed, the abbreviation which reads: M-moisture-moist wound management, O-oxygen-care for oxygenation of the wound bed tissues, I-infection and inflammation control-control of microbial load and inflammation, S-support-supporting the healing processes, e.g., by relieving the foot, T-tissue debridement/management-cleaning the wound from infected and necrotic tissues [24]. Proper care of ulcers is to ensure optimal conditions for their healing, antiseptic protection, and protect wounds against mechanical injuries. This means the necessity to conduct systemic treatment together with therapeutic actions directly at the site of damage. It is also very important to control the metabolic rate of diabetes, a proper diet, the use of appropriate specialist dressings, appropriate footwear, and insoles or orthotics to relieve the foot affected by the disease. Surgical treatment is also necessary in justified cases [24–27].

The conservative methods used in the comprehensive therapy of the diabetic foot syndrome include: VAC negative pressure therapy, the PRP method (bandages with the use of platelet-rich plasma), regular physical activity, and selected treatments in the field of physical medicine, which also include local ozone therapy and local oxygen therapy [25–29]. In the case of these two methods, increasing the partial pressure of oxygen in the tissues results in better oxygenation. Disturbed vascular flow, chronic

Table 1: Comparison of the percentage change in the area of ulcers and pain intensity after the end of the therapeutic cycle between the study groups, together with the statistical evaluation.

| | Topical oxygen therapy ($n = 42$) mean ± SD | Topical ozone therapy ($n = 43$) mean ± SD | $p$ |
|---|---|---|---|
| % change of ulcer surface area after treatment | 33.25 ± 10.97 | 28.67 ± 14.47 | 0.030 |
| % change of the VAS score after treatment | 57.13 ± 16.24 | 40.21 ± 14.53 | 0.001 |

inflammation, bacterial infections, and decreased locally metabolic oxygen production contribute to chronic hypoxia of the limb tissues. While acute, short-term hypoxia may indeed stimulate angiogenesis, chronic hypoxia inhibits not only angiogenesis but also the associated production of reactive oxygen species (ROS) necessary for regulating growth factors, cell signaling, and killing bacteria. Therefore, it seems that the application of selected physical treatments aimed at improving tissue oxygenation should be the right course of action. Oxygen is a rate-limiting substrate for many biochemical reactions and plays a key role in energy production and cellular metabolism. Daily sessions help to provide the treated area with the right amount of oxygen, thus contributing to the progression of the healing process from the inflammatory phase to the proliferation phase. The formation of new blood vessels in the process of neovascularization also depends on the correct level of tissue oxygenation [18, 30, 31].

In the presented study, after the use of local ozone therapy and local oxygen therapy, we achieved an improvement (intensification) of the ulcer healing process consisting in a statistically significant reduction in their surface area in both studied groups, while we found only a slight advantage of local oxygen therapy in this regard. Moreover, we confirmed a statistically significant analgesic effect of both compared methods. Based on the results obtained, it should be assumed that both compared methods may play an important role in the comprehensive treatment of patients suffering from diabetic foot ulcers. Taking into account that in both the group of patients a similar conventional treatment was used, it seems that the lack of classic control group consisting of patients subjected only to conventional treatment does not make a significant problem in interpretation of the obtained therapeutic effects in both compared groups.

Izadi et al. also confirmed the effectiveness of ozone therapy in 200 patients diagnosed with diabetic foot ulcers. The subjects were divided into two research groups. Group 1 was treated in addition to the standard local treatment also with the local application of ozone, while group 2 used only routine care for the diabetic foot. In the ozone group, all patients achieved complete ulcer healing. The mean healing time was 69.44 ± 36.05 days (range 15–180 days) [32]. The previous observations are also consistent with the results of the studies by Dhamnaskar et al. [33].

The results of our study are also consistent with the results of the analysis of available databases (Cochrane Library, PubMed, Ovid Embase, Web of Science and Chinese Biomedical Literature Database) carried out by Wen et al. concerning the evaluation of the effectiveness and safety of ozone therapy in the case of chronic wounds. The results of this analysis showed a statistically significant improvement in the use of ozone therapies in patients with ulcers in the course of the diabetic foot syndrome compared with patients treated with standard therapy in the control group, which concerned the reduction of the wound surface area and the reduction of the frequency of amputations [34].

A similar analysis of the available databases was carried out by Liu et al. assessing the effect of ozone therapy on the ulcer healing process in people with diabetes based on the included 3 randomized controlled clinical trials comparing the effects of ozone therapy with sham ozone therapy and other therapeutic interventions. In the first one, involving 101 patients, ozone treatment was associated with a greater reduction in ulcer area and shorter hospitalization than antibiotic treatment, but without a significant effect on the number of ulcers healed over the 20-dayfollow-up period. The other two studies involving 111 patients compared the effects of ozone treatment with the routine care of foot ulcers in people with diabetes. The results of the meta-analysis showed no significant differences between the groups in terms of ulcer area reduction, the number of healed ulcers, the frequency of adverse events and the frequency of limb amputation [35].

In another paper, the authors reported the case of a 52-year-old man with type 2 diabetes who suffered an injury to his right lower limb causing a deep wound. The patient was treated with ozone at a dose of 70 $\mu$g/dL for 30 days in 10 sessions (one 20-minute session every 3 days). The wound was fully healed after 1 month of treatment [36].

Baghid. et al. conducted studies to assess the effectiveness of ozone therapy in 60 patients with ulcers in the course of diabetic foot syndrome, showing no significant differences in age, sex, and type of diabetes. Treatments were performed twice a week for 10 weeks, and as a result of their application, a significant reduction in the duration of treatment and the size of treated ulcers was obtained [37].

In turn, Teguh et al. assessed the results of treatment with hyperbaric oxygen therapy (HBOT) in 134 patients diagnosed with a diabetic foot. The number of HBOT treatments was on average 48 over a period of 20–68 sessions. After HBOT treatment, 81% of all wounds were almost completely healed or completely healed, in 13% of cases the wound was stable, and only 2% required a major or minor amputation [38].

In another paper, the authors systematically reviewed 97 published studies on the effectiveness of treatment of diabetic foot ulcers (DFUs), taking into account articles on local interventions to improve the healing of DFUs published between June 2014 and August 2018. According to the authors, there was an improvement in the quality of research projects and a significant increase in the number of

Table 2: Comparison of the surface area of treated ulcers and the pain intensity in both the groups of patients before and after the end of the therapeutic cycle, taking into account the duration of the disease.

| | *Topical oxygen therapy* | | | *Topical ozone therapy* | | |
|---|---|---|---|---|---|---|
| | 1–3 years ($n = 26$) mean ± SD | 4–6 years ($n = 17$) mean ± SD | $p$ | 1–3 years ($n = 16$) mean ± SD | 4–6 years ($n = 26$) mean ± SD | $p$ |
| Ulcer surface area ($cm^2$) before treatment | 6.11 ± 1.19 | 7.30 ± 0.89 | <0.001 | 6.69 ± 1.18 | 8.11 ± 0.84 | <0.001 |
| Ulcer surface area ($cm^2$) after treatment | 4.01 ± 1.18 | 5.00 ± 1.18 | 0.015 | 4.55 ± 1.25 | 6.33 ± 1.54 | <0.001 |
| % change of ulcer surface area after treatment | 35.32 ± 9.94 | 31.98 ± 11.56 | 0.376 | 32.41 ± 12.85 | 22.95 ± 15.29 | 0.015 |
| VAS score (points) before treatment | 7.56 ± 0.72 | 8.07 ± 0.68 | 0.034 | 7.80 ± 0.98 | 8.11 ± 0.85 | 0.262 |
| VAS score (points) after treatment | 2.56 ± 1.15 | 3.92 ± 1.23 | <0.001 | 4.69 ± 1.22 | 4.76 ± 1.14 | 0.951 |
| % change of VAS score after treatment | 66.14 ± 14.89 | 51.58 ± 14.68 | <0.001 | 39.85 ± 14.72 | 40.77 ± 14.66 | 0.893 |

published works. Nevertheless, the evaluation and comparison of published studies remains difficult due to the clear clinical heterogeneity between studies regarding patient selection, duration of therapy, quality of standard care, as well as follow-up and description of clinical end-effects [39].

As Löndahl points out, currently HBO can be used as an adjunct therapy in a selected group of patients with difficult to heal wounds and ulcers in the diabetic foot syndrome, and according to the author, many studies are based on poor scientific evidence without specifying, for example, when to start and stop treatment which still remains to be clarified [40].

Currently, a serious problem is not only the diabetes epidemic itself and its health and social consequences but also the constantly growing economic costs associated with the treatment of diabetes complications, especially diabetic foot ulcer. The International Diabetes Federation (IDF) estimated that in 2013 these costs worldwide exceeded USD 827 billion [12, 41]. In Europe, direct and indirect costs related to the treatment of diabetes and its complications account for 3–5% of the budgets of European healthcare systems [23, 42].

In Poland, diabetic patients also generate high costs related to long-term medical care, which are on average two to three times higher than in nondiabetic patients. In addition, the costs of treating complications of diabetes are much higher than the cost of the disease itself-more than three times in hospital treatment [6, 41, 42.

One of the ways to solve problems of diabetic foot ulcers, which are common all over the world and have serious economic consequences are preventive measures leading to a reduction in the frequency of developing this complication, including, among others, an integrated approach to diabetes care with regular screening and patient education, which is low-cost and has the potential to reduce health care costs [43].

Unfortunately, patients with developed diabetic foot ulcers are a serious economic burden and the costs of their treatment increase with the severity of the disease. The cost of care for patients with diabetic foot ulcer is 5.4 times higher in the first year and 2.8 times higher in the second year after the first episode of this complication, compared to patients with diabetes without associated diabetic foot ulcers. In addition, the treatment costs for the most advanced ulcers are 8 times higher than for the treatment of low-grade ulcers [44].

That is why modern medicine is constantly looking for the alternative methods of effective treatment of chronic wounds, which are also cost-effective [12, 23].

Tiaka et al. reported that whole-body HBO procedures in the treatment of DFU are performed only in few centers due to the high cost of these procedures. Referring to the authors' conclusions, it should be noted that in our study, we used topical oxygen therapy with a pressure exceeding atmospheric pressure, for which the availability of treatments is much greater. In addition, the costs associated with the purchase of equipment are definitely lower in relation to single or multisite hyperbaric chambers [45].

Agarwal et al. confirmed that topical oxygen is a cost-effective procedure as the calculated cost of the therapy with the use of this method is about 42,000 INR (500 EUR) weekly [46]. This cost is similar as in our study.

In turn Dhamnaskar S. et al. reported that topical ozone gas therapy causes indirectly decrease of overall costs of treatment of patients with DFU as compared to the conventional management, mainly due to the faster rate of ulcer healing and early microbial negativity, resulting in reduction of duration of hospital stay and reduction in requirement of revision surgery [33].

Taking into account the moderate financial costs of topical oxygen therapy and topical ozone therapy procedures calculated in our study, as well as the above-mentioned reports of other authors it seems that both physical methods applied for the treatment of DFU could be considered as cost-effective.

Due to the advances in technology and medical engineering, devices for topical oxygen therapy and topical ozone therapy are becoming smaller, lighter, easy to use, and cheaper, which increases their availability also outside specialized hospital departments. It is also possible to transport them to a patient who may have mobility problems for various reasons.

Concluding, it I should be emphasized that our study is a new contribution to the field of physical treatment of diabetic foot ulcer mainly due to the following reasons.

As to our knowledge this study is the first one presented in available literature in which the direct comparison of the therapeutic efficacy and safety of topical ozone therapy and topical oxygen therapy in the treatment of diabetic foot ulcers was performed.

Moreover this study proved high therapeutic efficiency of both compared methods with regard to both stimulation of wound healing and analgesic effect in a prospective clinical trial conducted in the largest so far cohort of Polish patients with diabetic foot ulcers treated with those methods.

And what is especially important the results of this study confirmed that both compared methods are not only efficient and safe but also cost-effective and therefore they should be more widely applied in the treatment of diabetic foot ulcers in clinical practice.

*5.1. Limitations of the Study.* The work have some limitations, such as the relatively small size of the studied groups of patients, the lack of a control group subjected to treatment with the use of only conventional local pharmacological therapy without the simultaneous use of physical treatment, and lack of long-termfollow-up. The limitation of the study is lack of calculation of sample size.

## 6. Conclusions

The results of this original, prospective clinical study, which is pioneering for Poland, confirmed that the use of topical ozone therapy and topical oxygen therapy in patients with diabetic foot ulcers reduces the surface area of the treated diabetic foot ulcers, while local oxygen therapy shows only

a slight advantage in this respect. Moreover, both compared physical methods show a strong analgesic effect, which is significantly more effective in the case of local oxygen therapy. Moreover both applied physical methods appeared to be cost-effective due to relatively moderate financial costs of the treatment.

## Abbreviations

ATA: Total atmosphere
BMI: Body mass index
DFU: Diabetic foot ulcer
HBOT: Hyperbaric oxygen therapy
IWGDF: International Working Group on Diabetic Foot
PVD: Peripheral vascular disease
ROS: Reactive oxygen species
TOT: Topical oxygen therapy
VAS: Visual-analogue scale.

## Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethical Approval

The study was conducted in accordance with Declaration of Helsinki (1964) and its protocol has been accepted by the local bioethical committee at Medical University of Silesia in Katowice, Poland (approval reference number: KNW/0022/KB1/102/II/16/19). Every patient enrolled to the study has signed written informed consent approval for all procedures conducted in the study.

## Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

## Authors' Contributions

JP designed the study, performed data collection, performed data interpretation, prepared the manuscript, and performed the literature search. SSz performed data collection and performed statistical analysis. GC performed data interpretation.

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