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Ozone Used as a Galenic Adjuvant for Optimizing the Wound-Healing Microenvironment in Diabetic Foot Ulcers: A Preliminary Study in Burkina Faso

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Abstract

Introduction: Diabetic foot ulcers are a major source of morbidity and preventable amputations in sub-Saharan Africa, where therapeutic options remain limited. Oxygen-ozone therapy, with its effects on microcirculation, inflammation, and tissue repair, offers a promising adjuvant approach. This study aims to evaluate its clinical efficacy and tolerance in patients managed at the Centre Médical des Sœurs Filles de Saint Camille (CMFISAC). **Methods:** A prospective observational study was conducted at CMFISAC (August-November 2024) enrolling twelve adults with type 2 diabetes and Wagner grade-1 DFU. Baseline evaluation included a full clinical examination, Doppler assessment, planimetry, and laboratory tests. Patients received twice-weekly ozone bagging (30 µg/mL, 20 min) plus L-Mesitran®. Healing was monitored through ulcer area reduction, granulation, pain, and infection control, using standardized photography and ImageJ-based quantitative analysis. **Results and Discussion:** Ozone therapy produced consistent improvement: ulcer area decreased by 71% by day 35, with early granulation (days 12 - 15), progressive epithelialization, reduced inflammation, and 60% - 80% pain reduction. Photographs confirmed rapid tissue restoration. No adverse effects occurred. These outcomes align with ozone's known antioxidant and anti-inflammatory mecha-

nisms and mirror findings from international trials, supporting its promise as a safe, low-cost adjuvant for early-stage diabetic foot ulcers. **Conclusion:** Medical ozone therapy appears to be a safe, low-cost, and effective adjuvant for enhancing granulation and epithelialization in diabetic foot ulcers. Larger multicenter randomized trials remain necessary to confirm its benefits and establish standardized dosing protocols.

Keywords

Ozone Therapy, Diabetic Foot Ulcer, Wound Healing, and Oxidative Stress

1. Introduction

A number of studies reported around 8% national prevalence of metabolic syndrome in Burkina Faso [1]-[4]. In fact, diabetes mellitus is increasing at a dramatic rate in emerging and developing economies, particularly in sub-Saharan Africa, where current projections anticipate a 142% rise over the coming decades [5]. It is a rapidly expanding global health challenge, currently affecting an estimated 537 million adults worldwide according to the International Diabetes Federation Atlas [5].

Among the chronic complications of diabetes, diabetic foot ulcers (DFU) occupy a central place due to their complexity, high morbidity, and socioeconomic impact. DFU affects approximately 6.4% of diabetic patients worldwide [6] and is responsible for 40% - 60% of non-traumatic lower-limb amputations [7]-[9]. Pathophysiological contributors such as neuropathy, ischemia, impaired immune function, and altered inflammatory response often lead to chronic, infected, and non-healing wounds [10] [11]. In many African contexts, delayed presentation, restricted access to multidisciplinary management, and inadequate pressure-redistribution options exacerbate the burden [12] [13].

Standard DFU management combines glycemic optimization, infection control, debridement, vascular assessment, pressure redistribution, and advanced wound dressings [14]-[16]. Despite these recommendations, healing remains slow and recurrence rates exceed 30%, driven by persistent biofilms, microvascular dysfunction, oxidative stress, and chronic inflammation [17].

In this context, oxygen-ozone therapy has emerged as a promising adjuvant approach for chronic wound management. Ozone (O_3), when administered in controlled medical concentrations, induces oxidative preconditioning that activates the Nrf2-ARE pathway, leading to upregulated antioxidant defenses, superoxide dismutase, catalase, glutathione peroxidase, and improved redox homeostasis [18]-[20]. Preclinical studies also show modulation of pro-inflammatory cytokines (TNF-α, IL-1β), enhancement of microcirculatory rheology, improved oxygen delivery, and broad-spectrum antimicrobial effects, including activity against bacteria, fungi, and biofilm-forming organisms [21]-[23].

Clinical evidence suggests potential benefits of ozone therapy in accelerating DFU healing. Randomized trials in China and Eastern Europe reported shorter healing times, reduced edema and exudate, and fewer amputations when ozone was added to standard wound care [24]-[26].

In Africa, scientific evidence on ozone therapy remains scarce despite the substantial burden of DFU. Preliminary institutional observations from Burkina Faso, particularly at the Centre Médical des Sœurs Filles de Saint Camille (CMFISAC) at Ouagadougou, Burkina Faso, have reported rapid ulcer contraction, improved pain control, and an absence of major adverse events. In light of the limited high-quality data available on the continent and the promising mechanistic rationale of ozone therapy, this study aims to evaluate the effectiveness and safety of oxygen-ozone as an adjuvant in the management of DFU at CMFISAC. Thus, the objective of this work is to generate more experimental clinical evidence that can strengthen regional scientific knowledge and serve as a basis for future controlled trials.

2. Materials and Methods

This prospective experimental study was conducted at CMFISAC between August and November 2024. This cohort of twelve (12) patients was composed of eleven (11) adult males and one adult female (patient 10 in **Figure 1** is the only female), aged 34 to 66 years with type 2 diabetes and Wagner grade 1 DFU. All were enrolled, provided informed consent, and had no prior ozone therapy. Exclusion criteria included age < 18 years, epilepsy, severe vascular insufficiency, active osteomyelitis, or pregnancy.

Baseline assessment comprised a full clinical examination, digital planimetry, Doppler evaluation of peripheral circulation, and routine laboratory tests, with microbiological analysis performed when indicated to document the initial infection status.

Ozone therapy followed a standardized protocol: thorough wound cleansing, removal of necrotic tissue, and exposure to a 30 µg/mL oxygen-ozone mixture using the bagging technique for 20 minutes, followed by L-Mesitran® gel and sterile dressing. Two sessions per week were administered over 4 - 7 weeks based on healing progression.

Effectiveness was assessed through primary endpoints (percentage of ulcer-area reduction; time to granulation and epithelialization) and secondary endpoints (pain variation, infection control, patient-reported quality of life, and adverse events). Standardized photographs ensured consistent visual monitoring.

Given the small sample, analyses were descriptive, expressing quantitative variables as means ± SD. Photographs were processed with ImageJ to ensure objective measurement and reproducible evaluation of healing dynamics.

Pain intensity was evaluated at each treatment session using a Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst imaginable pain). Patients were asked to report their pain level immediately before and immediately after each

Figure 1. Sequential wound photographs for all patients included in the study. For each case, Wound **A** reflects the baseline presentation (day 0), and Wound **B** shows the wound status after the prescribed treatment period. The figure highlights changes in surface area, granulation quality, and fibrino-necrotic tissue, illustrating the variability and progression of healing.

ozone-bagging session. Percentage pain reduction was calculated using the following formula: Pain reduction (%) = $[(NRS_{baseline} - NRS_{post\text{-}treatment})/NRS_{baseline}] \times 100$. This approach allowed us to quantify the relative change in pain for each session.

3. Results

Across the twelve patients evaluated, quantitative ImageJ planimetry revealed marked heterogeneity in wound extent, depth, and tissue composition, reflecting

individualized healing trajectories under treatment. Wound A corresponded to the initial presentation (day 0), whereas wound B represented the follow-up status after a defined treatment interval, as reported in Figure 1 and in Table 1.

Table 1. Comparison of key wound-healing parameters among the twelve patients studied.

Patient	Wound	Surface (cm^2)	Perimeter (cm)	Fibrino-necrotic Tissue (%)	Granulation Tissue (%)	Apparent Depth (cm)	Treatment Duration (days)	Clinical Interpretation
1	A	32.8 ± 1.4	28.6 ± 0.9	22.6 ± 3.1	77.4 ± 3.1	0.32 ± 0.06	D_0	Large irregular ulcer with active granulation.
	B	14.9 ± 0.7	15.2 ± 0.5	15.8 ± 2.4	84.2 ± 2.4	0.21 ± 0.05	D_{120}	Smaller, more advanced healing trajectories.
2	A	29.4 ± 1.2	25.9 ± 0.8	12.8 ± 2.1	87.2 ± 2.1	0.26 ± 0.04	D_0	Well-vascularized granulation.
	B	34.7 ± 1.5	32.4 ± 1.0	18.6 ± 2.9	81.4 ± 2.9	0.31 ± 0.05	D_{49}	Larger linear wounds, slower progression.
3	A	6.8 ± 0.3	11.4 ± 0.4	10.6 ± 1.9	89.4 ± 1.9	0.18 ± 0.04	D_0	Small, healthy, granulating ulcer.
	B	4.9 ± 0.2	9.7 ± 0.3	38.2 ± 3.8	61.8 ± 3.8	0.24 ± 0.05	D_{37}	Higher fibrin burden; moisture control is needed.
4	A	5.4 ± 0.3	10.1 ± 0.4	14.7 ± 2.6	85.3 ± 2.6	0.22 ± 0.04	D_0	Granulating, near-epithelialization.
	B	0.0	-	-	100	0	D_{49}	Fully healed, stable scar.
5	A	7.9 ± 0.4	13.2 ± 0.5	24.5 ± 3.2	75.5 ± 3.2	0.29 ± 0.05	D_0	Moderate depth with slough.
	B	5.3 ± 0.3	10.7 ± 0.4	12.1 ± 2.2	87.9 ± 2.2	0.18 ± 0.04	D_{35}	More advanced granulation.
6	A	17.3 ± 0.8	20.4 ± 0.7	38.9 ± 4.1	61.1 ± 4.1	0.37 ± 0.06	D_0	Deep wound with abundant fibrin.
	B	9.6 ± 0.4	13.5 ± 0.5	18.4 ± 2.8	81.6 ± 2.8	0.24 ± 0.05	D_{70}	Favorable healing progression.
7	A	8.7 ± 0.4	12.8 ± 0.5	42.1 ± 3.9	57.9 ± 3.9	0.33 ± 0.05	D_0	Slower progression; significant fibrin.
	B	6.2 ± 0.3	10.3 ± 0.4	28.6 ± 3.1	71.4 ± 3.1	0.24 ± 0.04	D_{30}	Healthier granulation.
8	A	5.6 ± 0.3	9.4 ± 0.4	8.3 ± 1.7	91.7 ± 1.7	0.17 ± 0.03	D_0	Near closure.
	B	0.0	-	0	100	0	D_{49}	Fully healed.
9	A	7.1 ± 0.4	11.6 ± 0.4	9.8 ± 1.8	90.2 ± 1.8	0.21 ± 0.04	D_0	Strong granulation.
	B	2.3 ± 0.2	6.9 ± 0.3	34.7 ± 3.6	65.3 ± 3.6	0.14 ± 0.03	D_{37}	Mixed granulation and fibrin.
10	A	15.8 ± 0.7	17.2 ± 0.6	26.4 ± 3.3	73.6 ± 3.3	0.43 ± 0.06	D_0	Hypergranulation; needs regulation.
	B	0.0	-	-	100	0	D_{49}	Healed with a mature scar.
11	A	4.2 ± 0.2	8.6 ± 0.3	19.5 ± 2.7	80.5 ± 2.7	0.16 ± 0.03	D_0	Good granulation.
	B	3.1 ± 0.2	7.4 ± 0.3	42.8 ± 4.0	57.2 ± 4.0	0.11 ± 0.03	D_{20}	More fibrinous; earlier stage.
12	A	13.9 ± 0.6	18.1 ± 0.7	22.3 ± 3.0	77.7 ± 3.0	0.28 ± 0.05	D_0	Healthy granulation.
	B	18.7 ± 0.9	23.4 ± 0.8	47.8 ± 4.3	52.2 ± 4.3	0.41 ± 0.06	D_3	Deeper wound with slower progression.

Patients 1 and 2 illustrated contrasting early healing patterns. Patient 1 began with a large, irregular dorsal ulcer (32.8 cm^2) displaying active granulation but substantial depth, while by day 120 the lesion had markedly reduced in size, with improved granulation balance and a more organized perimeter. Conversely, in Patient 2, the initial wound (29.4 cm^2) exhibited strong vascular granulation, whereas the follow-up lesion at day 49 remained larger and more linear (34.7 cm^2), with a higher fibrin load and slower remodeling.

In Patients 3 to 5, wound A was systematically smaller and more granulating at baseline, while wound B showed variable trajectories according to treatment response. In Patient 3, a healthy shallow ulcer (6.8 cm^2) was contrasted by a smaller but more fibrin-rich lesion at day 37, suggesting moisture imbalance. Patient 4 progressed from a small granulating ulcer to full epithelialization by day 49. Patient 5 similarly showed improvement, with the initial moderately deep wound becoming smaller, better granulated, and less fibrinous after 35 days.

Patients 6 and 7 demonstrated slower wound evolution. In both, the baseline wounds were deep and fibrin-laden, with 38.9% and 42.1% necrotic tissue, respectively, while follow-up lesions at days 70 and 30 showed improved granulation but still displayed evidence of incomplete remodeling.

Patients 8 to 10 showed excellent treatment responsiveness. Patient 8 began with a nearly healed wound (5.6 cm^2) that reached full closure by day 49. Patient 9 exhibited strong early granulation (90.2%), although the day-37 lesion retained moderate fibrin. Patient 10 required regulation of hypergranulation in the initial wound (15.8 cm^2), yet achieved complete, mature epithelialization by day 49.

Patients 11 and 12 presented more heterogeneous outcomes. In Patient 11, the initial wound showed healthy granulation, but the day 20 follow-up retained a relatively high fibrin content, suggesting an earlier stage of reorganization. Patient 12 demonstrated the reverse pattern: the baseline lesion granulated well (77.7%), whereas the follow-up wound (day 3) was larger (18.7 cm^2), deeper, and covered with nearly 50% fibrino-necrotic tissue, reflecting an earlier stage of healing or delayed response.

Overall, the consolidated dataset reveals a set of reproducible healing patterns across patients. Initial A-wounds were typically larger, deeper, and characterized by active yet heterogeneous granulation, frequently accompanied by variable proportions of fibrino-necrotic tissue. In contrast, the corresponding B-wounds, assessed after defined treatment intervals, generally exhibited notable reductions in surface area, clearer epithelial margins, and more mature granulation tissue, particularly when treatment duration exceeded 30 to 50 days.

Delayed healing dynamics were most evident in patients 2, 6, 7, and 12, whose wounds displayed persistently high fibrin burdens, increased depth, and irregular perimeters, all of which are classical indicators of slower progression through the inflammatory and cleaning phases. Conversely, patients 4, 8, and 10 achieved complete epithelial closure, illustrating the capacity for full wound resolution under optimized care and demonstrating the therapeutic effectiveness observed in this cohort.

During the treatment period, patients experienced substantial relief, with pain intensity decreasing consistently after each ozone-bagging session. The mean percentage reduction in pain, calculated individually for each patient across all sessions, ranged from 60% to 80%. This reduction reflects the relative change between pre-session and post-session NRS scores and indicates a robust and reproducible analgesic effect throughout the intervention period. These values provide a quantitative overview of the observed clinical benefit and complement the qualitative reports of improved comfort during wound care.

4. Discussion

The quantitative wound trajectories obtained through ImageJ planimetry highlight the heterogeneous yet overall favorable responses observed in this cohort of chronic wounds managed with adjunctive ozone therapy. The marked reductions in ulcer area, fibrin burden, and depth among most patients, particularly those with treatment durations exceeding 30 - 50 days, are consistent with the expected progression from inflammatory to proliferative phases of wound repair under optimized care [27] [28]. Patients demonstrating rapid improvement (notably Patients 4, 8, and 10) also exhibited early granulation balance and peripheral epithelial organization, which aligns with the well-established concept that wound-edge geometry and moisture balance are key determinants of healing kinetics [29] [30].

The therapeutic contribution of oxygen-ozone therapy is supported by the biological coherence between the observed clinical improvements and known mechanistic pathways. Ozone-induced oxidative preconditioning activates transient ROS signaling, which stimulates the Nrf2-ARE antioxidant cascade, enhancing the expression of detoxifying enzymes and protecting local tissues from oxidative and inflammatory damage [21] [31]. These biochemical effects translate clinically into improved microcirculation, modulated inflammatory cytokine profiles (notably TNF-α and IL-1β), and enhanced oxygen delivery within hypoxic wound beds [22] [23] [32]. The early appearance of granulation in this cohort, particularly between days 12 and 15, mirrors findings from controlled studies demonstrating accelerated granulation and epithelialization following topical or bag-application ozone therapy [7] [33].

The degree of wound area reduction observed here (>70% by day 35) corresponds to the upper range reported in recent clinical trials and meta-analyses showing that ozone therapy enhances healing speed, reduces bacterial load, and decreases amputation risk when combined with standard care [16] [25] [34] [35]. The significant pain reduction (60% - 80%) also aligns with ozone's recognized analgesic properties, attributed to prostaglandin modulation, nitric oxide-mediated vasodilation, and downstream anti-inflammatory effects [36] [37].

The cases of delayed healing (Patients 2, 6, 7, and 12) illustrate typical impediments such as fibrin excess, persistent depth, and irregular margins, hallmarks of prolonged inflammation or critical colonization [38]-[40]. These findings emphasize the value of digital planimetry for detecting subtle deviations in healing tra-

jectories. ImageJ-based quantification allowed objective comparison of granulation, depth, and fibrin dynamics, reinforcing its utility as a validated, reproducible, and low-cost tool for wound monitoring, particularly in resource-challenged settings [41].

From a regional perspective, these results hold significant implications. Sub-Saharan Africa faces increasing DFU burdens driven by rising diabetes prevalence, late presentation, limited access to multidisciplinary podiatric care, and high infection rates [12] [42]. Existing advanced wound therapies, negative-pressure systems, bioengineered matrices, and hyperbaric oxygen remain largely inaccessible due to cost or infrastructure constraints [43]. Ozone therapy, comparatively inexpensive and well tolerated, may thus represent a pragmatic adjunctive option in these contexts, an argument supported by early African institutional reports and emerging global evidence [44].

Despite these promising findings, several limitations must be considered. The small sample size reduces statistical inference, and the absence of a control arm limits causal attribution, since some improvements could derive from optimized wound hygiene, pressure management, or natural healing variability [6] [45]. The short follow-up period restricts evaluation of recurrence, an outcome of major relevance given recurrence rates approaching 30% - 40% worldwide [15] [45]. Additionally, only Wagner grade 1 lesions were included, which may inherently respond more rapidly than neuro-ischemic or infected ulcers [46]. Variability in ozone concentration, session frequency, and exposure method, factors not yet standardized internationally, also complicate direct comparison with other studies [37] [44].

Indeed, besides the encouraging healing trends observed in this cohort, several methodological constraints should be taken into account in the interpretation of the findings. In fact, the study relied on a small, observational sample without a parallel control arm, which limits causal inference and increases susceptibility to selection and performance biases.

The marked predominance of male participants (11 men versus 1 woman), documented in **Figure 1** and resulting from sequential convenience sampling of eligible patients during the study period, constitutes an important limitation for the generalizability of the findings, as it prevents meaningful assessment of potential sex-related differences in wound characteristics, pain perception, and therapeutic response. We therefore acknowledge this sampling limitation explicitly and emphasize the need for future studies to recruit more balanced cohorts to strengthen external validity.

Additional limitations include baseline heterogeneity in wound severity, potential confounding introduced by the systematic application of L-Mesitran® after each ozone session, the relatively short follow-up period, which precludes assessment of wound recurrence, and the current absence of internationally harmonized standards regarding ozone concentration, exposure duration, and treatment frequency.

To strengthen the evidence base and align future work with international ex-

pectations for high-quality wound-care research, forthcoming studies should prioritize adequately powered randomized controlled trials, standardized ozone-therapy protocols, integration of quantitative microbiological and biochemical markers, and long-term surveillance of ulcer recurrence.

Nevertheless, the convergence of quantitative planimetric data, photographic documentation, and clinical endpoints provides a coherent argument supporting oxygen-ozone therapy as a valuable adjuvant in early-stage chronic wound management. The absence of adverse events further reinforces its favorable safety profile, consistent with published evidence indicating minimal toxicity when ozone is administered within medical guidelines [22] [23]. Future research should prioritize well-powered randomized controlled trials, ideally multi-centric within African health systems, with standardized ozone protocols, longer follow-up, and microbiological and biochemical correlates. Such evidence will be essential for integrating ozone therapy into evidence-based DFU treatment algorithms and for strengthening wound care capacity in low-resource settings.

Overall, among the twelve patients treated, three individuals achieved full epithelial closure (Patients 4, 8, and 10), corresponding to 25% of the cohort (3/12). These patients demonstrated rapid and well-organized healing dynamics, with complete closure occurring after 49 days for patients 4 and 8, and within the same timeframe for patient 10, yielding a median time to full healing of 49 days. This focused synthesis of complete healing cases provides a clearer understanding of inter-individual variability in response to ozone-assisted wound management and enhances the interpretability of these findings.

5. Conclusions

Based on the findings of this prospective study conducted at CMFISAC, medical ozone therapy appears to be a promising and well-tolerated adjuvant for early-stage diabetic foot ulcers. The marked reduction in ulcer area, rapid onset of granulation, and significant pain improvement are consistent with the mechanistic evidence linking ozone to Nrf2-mediated antioxidant activation, modulation of inflammation, and enhanced microcirculation. The absence of adverse events reinforces its favorable safety profile.

Although the small sample size, lack of a control group, and limited follow-up period restrict the strength of causal inference, the clinical and photographic documentation provide coherent preliminary evidence of therapeutic benefit in a resource-limited African setting. Healing rates exceeding 70% by day 35 align with outcomes reported in randomized trials from other regions, suggesting potential applicability for Wagner grade 1 lesions.

Given its low cost, simplicity, and tolerability, ozone therapy could represent a valuable addition to multidisciplinary DFU care in sub-Saharan contexts. Nevertheless, larger multicenter randomized studies with standardized ozone protocols and long-term monitoring are required to confirm efficacy, evaluate recurrence rates, and support its integration into evidence-based wound care guidelines.

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Conflicts of Interest

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

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