Ozone therapy for diabetic foot

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Abstract
Diabetic foot ulcers (DFU) are a burden to the diabetic community. With increasing medical bills, to unsuccessful treatment, those suffering from DFUs can use alternative therapeutics. First seen in the mid-1800s, ozone (O3) is thought to be unstable, due to inherent molecular nature. With the help of pharmaceutical science, various O3 treatments have flourished in the medical community to help those suffering from DFUs. Promising results are seen through numerous studies. Usually, a mixture of both O2 and O3 is seen in pressurized machines as administered to the foot ulcer. Foot ulcers, specifically DFUs, need to be assessed, cleaned, and treated as fast as possible for the fastest results. Such results can lead to the foot being treated as soon as possible. With fast growing clinical trials in O3 therapy and quick administration of the O3, O3 therapy may be on the rise to be at the forefront of treating DFUs. Compelling evidence is seen in clinical trials, but more must be done to fully understand the role of O3 in DFUs.

Key words: ozone therapy; wound closure; oxygen-ozone; diabetic foot ulcer; diabetes mellitus; Charcot foot; peripheral arterial disease; wound healing
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Introduction
Foot ulcers have an incidence of 4–10% in patients diagnosed with diabetes mellitus and a lifetime incidence of around 25%. Furthermore, it is clear that patients who present diabetic foot ulcers (DFU) are hospitalized more often than without DFU. Amputations can be attributed to ischemia, infection, neuropathy, faulty wound healing, ulceration, gangrene, and initial minor trauma. Recurrent infections in patients suffering from type 2 diabetes mellitus (T2DM) coupled with high planter pressure are a major determining factor for DFUs. Common treatments of DFU is debridement, offloading areas of friction and other conventional wound managements. If treatment is delayed, the neuropathic and vascular complications of DFU can lead to gangrene or even amputation. Not only is foot problems of diabetic patients seen as a major factor when considering morbidity, there seems to be a cost burden with heavy expenditure associated with treatment for the diabetic foot (DF). The use of ozone (O3) within the medical community has begun in the mid 19th century. Medicinal application of O3 is met with great discourse due to its inherently unstable nature. However, it is believed that O3 can be initiated to pharmaceutical science with great therapeutic benefit to specific biological systems and not just serve as an esoteric approach. O3 has been been seen to be used in many medicinal applications ranging from uses in dentistry to proper sterilization of medical instruments. Beneficial effects of O3 has been seen in orthopedics, mucosal and cutaneous infections. Future effects can show O3 therapy being used to treat heart failure. Furthermore, there is growing evidence that O3 can be used to treat DFUs. A study showed that O3 treatment via rectal insufflation can improve glycemic index along with preventing oxidative stress in diabetic rats. Efficacy can be measured by how well the wound has closed in DFU after O3 treatment has been administered. Herein we review the evidence for possible use of O3 therapy on DFU.

Classification of Diabetic Foot Ulcers
There are several different ways to assess the severity of a DFU. The most common classification system surfaced in the 1970s named the Meggit-Wagner classification, summarized in Table 1. The Meggit-Wagner classification system has been around the longest, however, some researchers believe it lacks overall substance to describe the ischemia and possible complications. In the early 1990s a more profound classification system, developed by the University of Texas, surfaced and is summarized in Table 2. Although these two classification systems are both very much used today, it is believed that the Meggit-Wagner classification is too simple and the University of Texas classification is too complex. That is until Amit Jain proposed a new classification based on infective and non-infective complications as depicted in Table 3.

Molecular Genetics of Diabetic Foot Ulcers
The Intelectin 1 (ITLN1) gene encodes a protein known as

| Grade | Clinical manifestation |
|-------|------------------------|
| 0     | Pain                   |
| 1     | Superficial ulcers     |
| 2     | Deep ulcers            |
| 3     | Ulcers involving bone  |
| 4     | Forefoot gangrene      |
| 5     | Full foot gangrene     |
Table 2: University of Texas classification system for diabetic foot ulcer\textsuperscript{15}

| Stage | 0 | 1 | 2 | 3 |
|-------|---|---|---|---|
| A     | Lesion completely epithelized (pre-/post-ulcerative) | Superficial wound | Wound penetration to tendon or capsule | Wound penetration to bone or joint |
| B     | Infection | Infection | Infection | Infection |
| C     | Ischemia | Ischemia | Ischemia | Ischemia |
| D     | Infection & Ischemia | Infection & Ischemia | Infection & Ischemia | Infection & Ischemia |

Table 3: Amit Jain’s classification system for diabetic foot ulcer\textsuperscript{16}

| Type | Lesion |
|------|--------|
| Type 1 (infective) | Cellulitis, abscess, necrotizing fasciitis, wet gangrene, osteomyelitis, tinea pedis |
| Type 2 (non-infective) | Skin and soft tissue: non-healing ulcer, bullae |
| Type 3 (mixed) | Bone/joints: Charcot foot, hammertoes, claw toes |
| Type 4 (vascular) | Vessel: peripheral arterial disease |
| Type 5 (nervous) | Infective and non-infective complications |

Diagnosis of Diabetic Foot Ulcers

Patients presented with DFUs are at risk for having peripheral arterial disease (PAD). Furthermore, nearly 50% of patients present with DFU are also present with PAD.\textsuperscript{21} A common physical examination for diabetic patients with foot ulcers is the use of ankle brachial pressure-systolic (ABI-s). The use of the ABI-s test is to understand how severe PAD has advanced in patients with DFUs. However, diabetic patients tend to have calcified lower limb arteries, disrupting the systolic pressure in the arteries after the contraction of the heart. ABI-s can be falsely elevated due to the calcified lower limb arteries. A study shows that instead of performing ABI-s one can perform ankle brachial pressure-diastolic (ABI-d). Asbeutah et al.\textsuperscript{22} had a size of 51 patients present with DFUs, 26 of which came present with calcified lower limb arteries and 25 of which did not present calcification. Another 25 persons were used as a control. Simply enough, both ABI-s and ABI-d were measured bilaterally via a brachial and ankle oscillometric pressure. The use of analysis of variance (ANOVA) showed statistical significance among people with the use of ABI-s and ABI-d leading to the conclusion that ABI-d may be a better tool for patients with DFUs with calcified arteries.\textsuperscript{23} More studies have been done to see whether other forms of non-invasive vascular assessment can be performed to assess PAD more significantly. Common device-based diagnostic testing for patients with DFU and possible PAD includes color duplex ultrasonography, MRI angiography, radiography, capillaroscopy, plethysmography, continuous wave Doppler (CWD) and toe-brachial index (TBI). Some researchers believe that ABI testing is not as effective as others such as CWD or TBI. A study was done where 117 participants were recruited with only 72 present with diabetes and 45 without diabetes. All patients received diagnostic testing via ABI, TBI, and CWD from the right lower limb. To properly assess accuracy a color duplex ultrasonography was used. Tehan et al.\textsuperscript{24} determined that CWD was both the most sensitive and most specific in determining the presence PAD in patients with diabetes than TBI or ABI. Another study ruled out against ABI because of the significant limitation it places on diabetic patients presented with critical limb ischemia.\textsuperscript{25}

Applying Ozone to Diabetic Foot Ulcers (Table 4)

A study demonstrated that ozonated water, along with ozonated oils, can be used as a disinfectant and healing stimulant.\textsuperscript{10,26} This can reap great benefit for individuals suffering from DFUs. Furthermore, O\textsubscript{3}-O\textsubscript{2} treatment can improve vascular endothelial growth factor (VEGF), transforming growth factor-\beta (TGF-\beta), and platelet-derived growth factor (PDGF) levels.\textsuperscript{27} The aforementioned growth factors, specifically, TGF-\beta, seem to increase in patients with DFUs and can heal the localized gangrene and tissue remodeling.\textsuperscript{28,29} O\textsubscript{3} causes platelets to aggregate, along with the release of the specific growth factors (e.g., PDGF, TGF-\beta, and IL-8) which is known to heal wounds rapidly.\textsuperscript{20} Furthermore, O\textsubscript{3} when applied to DFUs, eliminates pathogens and the O\textsubscript{3} promotes proliferation of...
fibroblasts. This helps rebuld the intercellular matrix, healing the area around the DFU. Bulymin et al. demonstrated that O₃ has antibacterial properties and developed a new method for treatment via hydropressive treatment of wounds. A stream of ozonized fluids is generated under a pressure of 350 ATM and an “OZh-2” apparatus is used. The wound is cleansed of ozonized fluids is generated under a pressure of 350 ATM for treatment of wounds. A stream is directed to the area around the DFU. Bulynin et al. demonstrated that one should wear proper footwear to alleviate unnecessary pressure to the foot. In non-healing wounds, a combination of O₂-O₃ therapy might be beneficial. Proper debridement of the area around the DFU is a key step in beginning the healing process. One study showed that the use of hyperbaric oxygen therapy can ameliorate dermal wound healing. Travagli et al. believed that the accelerated trend of wound closure in a young population may be due to O₂ tension by O₃ in the surrounding wound area that acts as an antibacterial substance to decrease bacterial infection. In the late 20th century, a team of German scientists used O₂ on skin ulcers caused by diabetes. They used a polythene-bag for 25 minutes on average with a concentration ranging from 10 to 80 μg/mL. The different concentrations aforementioned were used with how severe the ulcers were. As the patients’ ulcers healed, a lower concentration of O₃ was used. Záhumenský et al. stated that offloading and debridement of the area around the DFU is a key step in beginning therapy for neuropathic ulceration. Furthermore, the healing process can be accelerated by O₂, however, one should wear proper footwear to alleviate unnecessary pressure to the foot. In non-healing wounds, a combination of O₂-O₃ therapy might

### Table 4: Studies testing ozone for diabetic wound care

| Study            | Route of administration of O₃ | Type of study            | Patients information & sample size | Measured parameter | Findings                                                                 |
|------------------|-------------------------------|--------------------------|------------------------------------|--------------------|-------------------------------------------------------------------------|
| Wainstein et al. | Ozoter 101 device a noninvasive sealed chamber using O₂-O₃ mixture | Randomized, double-blind, placebo-controlled clinical trial | n = 61, 62% male, average age 62.6 with a standard deviation of 9.8 years old | Wound size         | Per protocol (PP): Ozone groups vs. placebo group: P = 0.03 ozone group significantly higher rate of wound closure. Ozone group with wound size < 5 cm versus sham group: P = 0.006 for total wound closure in ozone group and 50% in sham group |
| Rosul et al.     | Phase 1: 96% O₂ & 4% O₃ at 80 μg/mL 4 times a week for 4 weeks. Phase 2: 98% O₂ & 2% O₃ at 40 μg/mL until week 12 | Case study with two groups | n = 47                           | Wound size, level of lipid peroxidation and antioxidant protection indexes, length of hospital stay | Group A vs. Group B observations: Significant rate of wound healing, lipid peroxidation, reductions of hospital stay, greater antioxidant protection |
| Rosul et al.     | Group B received traditional therapy. Group A received traditional therapy along with systemic and regional ozone therapy for 12–14 days, one session per day. Local wound treatment by ozone at 4000 μM/L | Caste study, ungrouped | High-level of colonization by microorganisms n = 49 | Density of microbial colonization | Yielded significance in decreased microbial colonization of wounds |
| Martinez-Sanchez et al. | Group 1 treatment: 20 sessions of ozonization (50 mg/L) and local treatment via sealed bag with ozone (60 mg/L). Group 2 treatment: topical and systemic antibiotics | Randomized, grouped, controlled, clinical trial | n = 101, group 1: n = 52, group 2: n = 49 | Wound size, glycemic index, endothelial damage via oxidative stress | Group 1 vs. Group 2 observations: Healing of lesions improve significantly in group 1, fewer amputations seen, no side effects observed, reduced hyperglycemia |
| Zubarev et al.   | Controlled group: underwent operative treatment and standard local treatment along with low-frequency ultrasound. Treatment group: underwent ultrasonic cavitation and ozone therapy of the wound | Grouped case-study | n = 120 with a control of n = 90 | Ablation of wound, microbial contamination, decontamination | Treatment group vs. controlled group observation: Decreased microbial contamination, facilitations of growth, prolonging of decontamination |
| Zhang et al.     | Ozone group: non-invasive oxygen-ozone treatment with 52 μg/mL ozone (total volume 20–50 mL) via special bag for 30 minutes per day for 20 days via ozone generator device + standard treatment Control group standard treatment: debridement once every 2 days and wound dressing | Randomized controlled clinical trial | n = 50, control group and ozone group. Baseline values not significantly different in wound size | 4-Leveled therapeutic effect on wound closure, expression of vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF) | Ozone group had a 92% significant effective rate compared to 64% for the control group (P = 0.037). Ozone group had significantly smaller wound size at day 20 (P = 0.001), more collagen fibers (P = 0.012), VEGF, and PDGF levels significantly higher (P < 0.05), significantly higher TGF-β, at day 11 (P < 0.05) |
be of benefit. A study showed that it can heal and reduce the pain due to the inherent disinfectant properties and scavenging properties of endogenous oxygen free radicals. O$_3$ is recognized as a disinfectant because it is known to inactivate bacteria by destroying their envelope through oxidation of specific proteins and lipids. Moreover, interferon, TNF, and IL-2 activate the immune system. This can explain why a reduction in infection is seen when O$_3$ therapy is used for DFUs. A few studies showed that when patients come present with orthopedic wounds, O$_3$ therapy can be applied after initial conventional treatment.

SAFETY OF OZONE THERAPY

The utility and safety of intralesional O$_3$ injection in the treatment of chronic wounds has not yet been reliably assessed. Though O$_3$ therapy is typically safe without adverse reactions, it may be toxic if administered outside its therapeutic window. Because intralesional O$_3$ injection has not yet been used in any of the studies involving DFUs, its safety has not yet been ascertained. These injections may inadvertently drive the superficial infection into the deeper tissue. Moreover, O$_3$ therapy is not recommended for deep, heavily infected or necrotic wounds.

Uzun et al. described a case of a diabetic patient who developed severe foot necrosis and infection after receiving intralesional O$_3$ injections for a non-healing wound. Major complications that have been linked to O$_3$ injections for lumbar disc herniation include vitreo-retinal hemorrhages, ventral and dorsal root injury, pyogenic discitis, and ventral epidural abscesses, and fulminant septicaemia and death. Skin irritation may follow topical O$_3$ application while respiratory irritation may occur due to gas emitted from the generator. In O$_3$ therapy via autotransfer for psoriasis, Marchetti et al. described a fatal gas embolism. When tested in pregnant rats, teratogenic or embriotoxic effects (i.e., fetal malformations) of O$_3$ administered via rectal insufflation have not been identified. In the end, to prove the innocuity of O$_3$, more controlled clinical trials are warranted.

PREVENTIVE CARE

Common measures individual can take to prevent DFUs is to get an annual DF screening along with care intervention, especially those at high risk of DF complications. Another measure, limited to individuals who have experienced ulceration, is nerve decompression surgery. It can prevent further ulceration along with amputation. PAD is a major complication of DF and can determine the prognosis of healing. According to the Eurodiale study group, a neuropathic ulcer shift to neuro-ischemic ulcer is quite often. Assessing PAD via imaging and revascularization can dramatically reduce health risks if treated appropriately and on time. Diabetic neuropathic ulcers can be managed by removing calluses, controlling infection, and reducing the amount of weight placed on the afflicted foot. Many physicians agree that one of the greatest ways to decrease rates of mortality and morbidity among those who suffer from DF complications is early recognition. Holistic care is available across the world via Multi-Disciplinary Foot Clinics. Callus formation in DF patients serves a high level of predictability of ulcer formation. One can remove such calluses via urea-based preparations. It behooves patients to consider preventative measures because a study has shown individuals with DFUs have a poor health-related quality of life.

CONCLUSION

The purpose of this review is to provide the scientific community with up-to-date clinical trials, peer-reviewed studies, and compelling evidence on O$_3$ therapy in the treatment of DFUs. Further studies with a larger sample size would corroborate existing evidence.

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