INTRODUCTION

A recognized, staggering statistic is that every 30 s, somewhere in the world, a lower limb is lost because of diabetes.1 Approximately 11% of the population in the United States, or 37 million people, have diabetes. Diabetic foot ulcers (DFUs) will develop in one-quarter of patients with diabetes,2 and five of every 1000 people with diabetes (i.e., 185,000) will experience lower extremity amputations.3 Upward of 85% of amputations are preceded by foot ulcers, and those patients with a lower extremity amputation have a diminished quality of life.4

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In one study of approximately 3400 U.S. veterans during the period 2004–2010, the cost of a lower leg amputation (LLA) rose from $50,341 to $60,647, and annual costs on the VA system rose from $170M to over $200M. Those costs were for the actual LLS procedure only and did not include LLA-patient recovery, LLA-patient lifetime support, or LLA-patient consequential comorbidity costs. Of public health concern, the incidence of DFUs is disproportionately higher in ethnic minorities and in those from disadvantaged socioeconomic backgrounds. There is growing evidence that despite high caloric intake, DFU patients lack the requisite micronutrients to enable wound healing. Nutrition is often overlooked in the multidisciplinary approach needed for wound optimization, but micronutrients are very important for healing complex wounds. However, DFU patients are not the only ones who experience failure in wound healing, necrotic tissue accumulation, and tissue excision/reconstruction. Ulcers and amputations have profound quality-of-life consequences because of diminished physical function, loss of employment/income, emotional suffering, including depression, and social isolation. The problem is that there have been no reliable therapeutic approaches for the complex problem of refractory wounds with increasing necrotic tissue, resulting in amputations.

**Aims and objectives**

The purpose of this research is to inform wound care providers about the remarkable healing results on two totally different patients; one was scheduled for a frontal foot amputation, and the other patient was scheduled for an umbilicus reconstruction. Both patients presented long-term, refractory wounds with accumulating necrotic tissue. However, after a 5-week therapeutic regimen for the DFU patient and an 8-week therapeutic regimen for the patient with the necrotic umbilicus, wound healing, wound closure, and positive outcomes were evident. Both patients were able to avoid undesirable surgical procedures and expressed gratitude for their improved quality of life. Also included are the details and contrasting outcomes from a third patient case, where the patient only received hyperbaric oxygen treatment (HBOT).

Although the approach for every complex wound care patient is multidisciplinary, the conceptual framework for this paper includes an emphasis on the successful implementation of trifurcated therapeutic approach, including (1) specific nutritional supplementation and diet alteration, (2) the application of a patented, high potency HA wound gel formulated with a specific HA molecular weight and a stabilizing, non-ionic polymer matrix, and (3) patient exposure to HBOT at prescribed intervals.

**MATERIALS AND METHODS**

The physician investigator conducted this qualitative method case study during her regular professional medical practice. She selected study subjects based on the exigency of patients’ needs. The three subjects selected met three inclusion criteria. The first inclusion criterion was that the patient had at least one serious refractory wound, which wound did not respond to any previous treatment regimens at any treatment center. The second inclusion criterion was that significant necrotic tissue was evident in the wound(s). The third inclusion criterion was that each patient was facing traumatic surgical intervention—either amputation or excision with reconstruction.

The study lasted 4 months during the period November 2022 through March 2023 and each patient received the novel trifurcated treatment regimen including (1) specific nutritional supplementation and diet alteration, (2) the application of a patented, high potency HA wound gel formulated with a specific HA molecular weight and a stabilizing, nonionic polymer matrix, which coincided with dressing change intervals (i.e., BID, TID, titrated down to a few as 3 times per week), and (3) patient exposure to HBOT at individually prescribed concentrations and intervals. The investigator measured wound diameters and tracked time to wound closure and wound healing. In addition, the investigator noted patient comments during the wound healing process and satisfaction comments when the wounds were healed.

**LITERATURE REVIEW**

**Nutrition in wound healing**

The role of nutrition in wound healing may be overlooked or minimized by some healthcare professionals but given the prolonged potential for the wound healing process, nutrition should be considered in wound prevention, wound preparation, and in acute and chronic wound treatment. Suboptimal nutrition can deleteriously affect immune function, collagen synthesis, and wound tensile strength, all essential in wound healing.

Wounds are highly variable, but some nutritional principles are generalizable for the benefit of all wound patients. The study results in the literature indicate that some nutrients are necessary only if deficient, and other nutrients are essential and therapeutically advantageous. Nutritional components can support wound healing through the inflammatory, proliferative, and remodeling phases of wound healing. In addition, nutritional components are important in mitochondria structure and function and mitochondria coordinate the stage-specific processes in macrophages, which are foundational for wound healing.
**Carbohydrates, fat, protein, and fluid**

Caloric needs during wound healing are estimated at 30–35 kcal/kg. Carbohydrates stimulate insulin production, which is helpful in the anabolic processes of wound healing, particularly during the proliferative phase. However, hyperglycemia can reduce granulocyte function and increase infectious complications. In the context of this study, the physician-investigator used dairy and gluten food elimination to help reduce inflammation and shock the cell messaging system to revert the wounded tissue from chronic inflammation to the proliferative phase.

Dietary fat intake is important for absorbing fat-soluble micronutrients, such as Vitamin A, omega-3, and omega-6 fatty acids. Omega-6 fatty acids are important to produce chemical mediators during the inflammatory response, such as prostaglandins and leukotrienes, resulting in platelet aggregation and inflammatory vasoconstriction. Omega-3 fatty acids dampen inflammatory responses and result in vasodilation through cytokine release. Although the overall effect of essential fatty acids on wound healing is still unclear, supplements during the inflammatory phase in a 1:1 ratio of omega-6 to omega-3 have been beneficial. Sufficient fat intake in acute or chronic wound patients can provide additional energy to the wound healing process, including structural aspects such as axonal myelination, cell lipid bilayers, and organelle membranes during tissue growth.

Protein is essential for all stages of wound healing, including immune function, collagen synthesis, angiogenesis, fibroblast proliferation, tissue remodeling, and wound contraction. Depletion of protein and minerals has been associated with an increased risk of developing chronic ulcers, hair loss, and nail dystrophies, and protein deficiency may result in impaired fibroblast proliferation, collagen synthesis, and prolongation of the inflammatory phase of healing. Protein-calorie malnutrition is a form of malnutrition marked by decreased calories and inadequate dietary protein intake, often resulting in deficient lean body mass. In addition, white blood cells, including leukocytes, monocytes, lymphocytes, and macrophages, require protein for their structure and function in the immune response.

Protein is also important in the maintenance of oncotic pressure important when treating venous insufficiency wounds because peripheral edema will exacerbate extraluminal pressure and slow wound healing. Furthermore, if there is insufficient dietary protein intake, the body may divert protein reserves away from wound healing processes for other body functions, resulting in a prolonged healing process. The presence of a wound increases protein demand by up to 200% and caloric demand by up to 50% to maintain adequate LBM stores. In addition, protein can be lost through wound exudate, and fluid balance should not be compromised.

Fluid in wound healing is important for maintaining skin turgor and facilitating tissue perfusion and oxygenation. In addition, water is a diluent for glucose, waste removal, and transport of micronutrients. Recommended fluid consumption is approximately body weight × 0.5 = ounces of water per day, which is 100 ounces or approximately 3 quarts/day for a person weighing 200 pounds.

**Important amino acids in wound healing**

The wound care professional should consider the dietary importance of amino acids, vitamins, and minerals when evaluating the wound patient. Of particular interest are arginine and glutamine, both of which have been shown to augment wound healing. Arginine is a conditionally essential amino acid and arginine supplementation may be required in increased demand (e.g., patients with sepsis, trauma, or wounds). Arginine is important for producing nitric oxide and collagen and has been effective in wound healing for more than three decades. In addition, arginine has been shown to increase lymphocyte mitogenesis and, with ornithine, also stimulate the production of growth hormone and the activation of T cells. Glutamine is also conditionally essential and can be manufactured endogenously, but stressful conditions may require supplementation.

In addition to the importance of arginine and glutamine in wound healing, β-hydroxy-β-methylbutyrate (HMB) plays an important role in wound healing. HMB is the bioactive metabolite of the essential amino acid, leucine, which has been shown to inhibit muscle proteolysis and modulate protein turnover. Interestingly, HMB supplementation in humans, when combined with exercise, results in increased muscle mass accretion.

In an interesting double-blind, randomized study, researchers were able to measure the effects of amino acid dietary supplementation on collagen production by measuring the collagen deposition in two small, sterile polytetrafluoroethylene tubes, they implanted into the deltoid region of elderly study subjects. Daily supplementation of 14 g arginine, 3 g HMB, and 14 g glutamine (total nitrogen 3.59 g) in two divided doses was administered to the experimental amino acid mixture group, and in the control group, subjects received an isonitrogenous, isocaloric supplementation of nonessential amino acids. Investigators measured catheters for hydroxyproline increases, indicating collagen accumulation, and α-amino nitrogen, an index measuring total protein deposition.

After 14 days, OHP measurements in catheters indicated a statistically significant enhancement of produced...
collagen (P<0.03), which was 67% more than the collagen produced by the control group. Investigators concluded that collagen synthesis is significantly enhanced in healthy elderly volunteers by the oral administration of a mixture of arginine, HMB, and glutamine. This provides a safe nutritional means for increasing wound repair in patients.\textsuperscript{17}

**Important vitamins in wound healing**

Vitamins in wound healing have been evaluated extensively, especially regarding their cofactor roles in enzymatic processes related to wound healing. Virtually all B vitamins are helpful in wound healing. Specifically, Vitamins B1, B2, B3, B5, B6, B7, B9, and B12 aid in the production of energy, DNA synthesis, and the production and function of cells and tissues in the human body, including the skin.\textsuperscript{21-32} Vitamin A functions mostly through nuclear retinoic acid receptors and regulates the growth and differentiation of many cell types within the skin. In wounded tissue, Vitamin A stimulates epidermal turnover, increases the rate of re-epithelialization, and restores epithelial structure. Retinoids can also reverse the inhibitory effects of anti-inflammatory steroids on wound healing. Retinoic acid has also been shown to enhance the production of extracellular matrix components (collagen Type I and fibronectin), increase the proliferation of keratinocytes and fibroblasts, and decrease the levels of degrading matrix metalloproteinases.\textsuperscript{35} Deficiency of Vitamin A results in altered B cell and T cell function and antibody production during the inflammatory phase and impaired collagen synthesis in the remodeling phase.\textsuperscript{11}

Vitamin C is purported to influence collagen formation, immunomodulation, and antioxidant functions. Vitamin C is also important in neutrophil migration and lymphocyte activation.\textsuperscript{14} Literature recommends 500–1000 mg of Vitamin C daily for wound healing, up to 2 g/day for severe wounds and burns.\textsuperscript{11} Vitamin C is an essential co-factor for collagen biosynthesis.\textsuperscript{1} Vitamin C is essential because humans are unable to synthesize Vitamin C, which must be strictly obtained through the dietary intake of fruits and vegetables.\textsuperscript{34} A growing body of evidence indicates that short-term high-dose Vitamin C in selected patients may improve hemodynamic parameters, decrease fluid resuscitation requirements in burn patients, reduce the incidence of perioperative atrial fibrillation, improve pain, reduce sepsis-associated mortality, and benefit patients with immune-enhancing antioxidant, and anti-mutagenic effects.\textsuperscript{21} To enhance collagen synthesis and other health benefits, the physician-investigator in this study supplemented patients with Vitamin C cofactor.

Vitamin D has been shown to induce cathelicidin, which is an antimicrobial peptide helpful in wound healing. In an interesting double-blind, placebo-controlled study (30 DFU patients in each study arm), investigators demonstrated that after 12 weeks of intervention with 50,000 IU given every 2 weeks, compared with the placebo, Vitamin D supplementation significantly reduced ulcer length.\textsuperscript{35} Investigators concluded that for patients with DFUs, Vitamin D supplementation for 12 weeks for patients had beneficial effects on glucose homeostasis, total-, low density lipoprotein-, total-/high density lipoprotein-cholesterol, erythrocyte sedimentation rate, hs-C-reactive protein, and malondialdehyde levels. The investigators also opined that vitamin D may have played an indirect role in wound healing due to its effect on improved glycemic control.\textsuperscript{35}

**Important minerals in wound healing**

Minerals are also essential micronutrients, especially with respect to enzyme structure. Zinc, for example, has more than 200 zinc-containing enzymes, including superoxide dismutase, involved in wound healing, which function as antioxidants and modulate cell replication, nucleic acid metabolism, tissue repair, and growth. Zinc is a cofactor for many metalloenzymes required for cell membrane repair, cell proliferation, growth, and immune system function. The pathological effects of zinc deficiency include the occurrence of skin lesions, growth inhibition, impaired immune function, and compromised wound healing.\textsuperscript{36} Insufficient zinc levels can result in decreased cytotoxicity of natural killer cells, impaired phagocytosis in macrophages and neutrophils, and decreased number of granulocytes. However, excess zinc supplementation can interfere with the absorption of other cations, such as iron and copper. Zinc dietary supplementation should be avoided if there is no deficiency. Noteworthy is that alcohol consumption impairs antioxidant defense, and zinc was noted to be decreased in male alcoholics.\textsuperscript{37}

Selenium has been postulated as beneficial in wound healing and selenium levels have been shown to be affected by alcohol consumption.\textsuperscript{37} Dietary supplementation can improve zinc levels.\textsuperscript{36} Dietary suplementations can improve selenium levels.\textsuperscript{38}

**Summary of carbohydrates, protein, fat, and supplementation of amino acids, vitamins, and minerals**

Data support evaluating the patient’s nutritional status and ensuring sufficient calories from a balanced diet of carbohydrates, fats, and protein. Supplemeneting protein, fluid, and Vitamins A, C, and D should be done as needed at recommended dosages. However, as discussed below, relevant to mitochondrial energy production, thiamin, riboflavin, niacin, lipoic acid, and pantothenic acid are also necessary. Deficiencies in arginine, glutamine, and zinc should also be considered, and the data gathered in this literature review support supplementing these micronutrients in deficiency states.
Mitochondria roles in wound healing - impacted by nutrition

There has been an increasing trend of mitochondrial dynamics research during the past 20 years. In one literature review, there were 4576 publications between 2002 and 2021 in the Web of Science database, with most of the literature contributions coming from the US. Mitochondrial energy disruptions can contribute to a wide range of metabolic disturbances and symptoms, including fatigue, immune system dysfunction, dementia, depression, behavioral disturbances, attention deficiency, muscle weakness and pain, angina, heart disease, diabetes, skin rashes, and hair loss. Metabolic energy production mechanisms apply in these conditions and may benefit from nutritional strategies that optimize energy production and metabolic pathways.

Each cell in the body, with the exception of mature red blood cells, contains between 500 and 2000 mitochondria, whose function is to convert and store energy found in nutrient molecules to adenosine triphosphate (ATP). Vitaly, humans cannot survive for even 1 s, without a constant supply of ATP. In the Krebs’ cycle, acetyl coenzyme A is converted to citric acid and after a series of biological oxidations, free hydrogen ions combine with oxygen to produce ATP and water as the end products.

Most of the products of protein, carbohydrates, and fat metabolism are reduced to the molecule acetyl coenzyme A, which enter the Krebs’ cycle at different points. The primary fuel in the body is glucose, which metabolized into pyruvic acid and then into acetyl coenzyme A, but amino acids and some chained fatty acids can also be metabolized into the Krebs cycle.

Interconversions of Krebs’ cycle intermediates are controlled by enzymes that often require vitamin-derived cofactors and minerals to operate. For example, pyruvate conversion to acetyl-CoA requires cofactors derived from thiamin, riboflavin, niacin, lipoic acid, and pantothenic acid. A deficiency in these nutrients can disrupt mitochondrial energy production.

B vitamins, including pyridoxal-5-phosphate, folate, and methylcobalamin, also facilitate the production of DNA and energy. Regarding acids, in addition to citric acid, pyruvic acid, and pantothentic acid, as mentioned previously, researchers have also found that alpha-ketoglutaric acid, malic acid, fumaric acid, and succinic acid can stimulate a high yield of ATP from the mitochondria for tissue energy (which can be beneficial for wound healing).

Interestingly, regarding diet and mitochondrial function, diet-induced obesity is associated with impaired mitochondrial function. Mitochondria organelles are highly dynamic, and the balance in fusion/fission is contingent upon their bioenergetics. Fusion processes optimize mitochondrial function, whereas fission processes are associated with the removal of damaged mitochondria. Mitochondrial fusion has a protective function, leading to an exchange of mitochondrial DNA and delaying apoptosis. In one study where investigators used transmission electron microscopy to examine and display intracellular microscopic differences, the authors noted that although endoplasmic reticulum (ER) and mitochondria function with different cellular roles, the organelles also interact with each other at sites (i.e., mitochondria-associated ER membranes; MAMs). MAMs are essential for calcium, lipid, and metabolite exchange. The authors demonstrated that in the liver, obesity leads to a marked reorganization of MAMs, which results in mitochondrial calcium overload, compromised mitochondrial oxidative capacity, and augmented oxidative stress.

Dietary fat sources affect mitochondrial dynamics and bioenergetics. Opposite to the effects of saturated fatty acids, omega-3 polyunsaturated fatty acids induce fusion processes and improve mitochondrial function. In one model, eicosatetraenoic and docosahexaenoic acids increased the expression of Mfn2 (mitochondrial fusion), and ATP levels and decreased oxidative stress.

The different effects of saturated and unsaturated fatty acids on mitochondrial morphology and dynamics were reported in vitro in C2C12 skeletal muscle cells. The results showed that treatment with saturated fatty acids induced mitochondrial fragmentations, but unsaturated and polyunsaturated fatty acids protected against mitochondrial fission.

Furthermore, the pro-longevity effect of caloric restriction has been correlated with changes in mitochondrial dynamics leading to decreased cell oxidative injury. Investigators have demonstrated that high-fat diets rich in saturated fatty acids result in hepatic fat accumulation and insulin resistance, which impair mitochondrial function and increase reactive oxygen species (ROS) production.

Summary regarding mitochondria roles in wound healing - impacted by nutrition

Mitochondria fusion can augment the wound-healing efficacy of macrophages. Mitochondrial bioenergetics are contingent on dynamic processes that nutrient intake and availability affect. A diet that does not lead to obesity but consists of a balance of carbohydrates, proteins, and fats (especially polyunsaturated fatty acids), acetyl coenzyme A, B vitamins, and specific acids favorable for ATP production may expedite the wound healing process.
HA in wound healing

HA is a major component of the extracellular matrix. HA possesses hygroscopic and viscoelastic properties, which play a pivotal role in the wound healing process. Beyond HA's structuring function, HA is actively involved in all stages of wound healing, including inflammation, granulation, remodeling, and re-epithelialization. As a non-immunogenic molecule, when highly purified, HA is currently used in routine local treatment of chronic wounds to promote tissue healing.

In an adult human with a weight of 70 kg (approximately 154 lbs), the amount of HA is approximately 15 g, but more than 50% of this amount is in the skin – mostly in the intercellular space of the dermis. Although HA was discovered early in the 20th century, because of HA's versatile properties, including biocompatibility, non-immunogenicity, biodegradability, viscoelasticity, and [controversial] antioxidant activity, HA has endured as one of the most studied and biologically modified molecules in modern medicine. Diapedesis is an important stage of leukocyte migration, which occurs during the inflammatory process of wound healing and HA has been shown to facilitate the healing roles of macrophages, mast cells, and dendritic/Langerhans cells as regulators of wound repair during the inflammatory, proliferative, and remodeling phases of wound healing. HA derivatives are currently used in many different biomedical applications, including arthritis treatment, ophthalmology, tissue engineering, and wound healing, and are being tested for use in more efficient drug-delivery systems in various advanced forms such as hydrogels or nanoparticles. Future researchers may focus more on the relationship between HA and ROS elimination, the role of HA in inflammation regulation, radio protectivity, and tissue damage/regeneration.

A significant number of HA products are marketed in the US. A review of PDAC (2023) listed codes revealed that wound care products consist of 0.2% HA potency in gel form or 0.2% to 0.5% HA when combined with a gauze pad. The literature is replete with HA studies in wound care, many of which have a small number of study subjects. One difficult aspect regarding subject recruitment is that wounds are diverse and not standardized, and so the consideration of multiple, uncontrollable independent variables becomes problematic when recruiting study subjects and when analyzing study intervention results.

However, in one study with 89 patients in a multicenter, randomized, double-blind design, investigators evaluated the efficacy and safety of an 0.5% HA-containing gauze pad and of its neutral vehicle. The trial lasted for 60 days and included once daily wound cleaning and gauze pad application. The authors concluded that for patients with leg, venous, or mixed origin ulcers, a statistically significant greater reduction in wound size was obtained after 45 days of treatment with the HA-containing gauze pad compared with the neutral vehicle (73±4.6% vs. 46±9.6% respectively; P=0.011). In local treatment of venous leg ulcers, HA gauze pad was significantly more effective than the neutral vehicle on wound size reduction, healed ulcer rate, and pain management, with a good safety profile.

In an interesting scientific study of HA published in Polymers, the scientists noted that the HA molecule is unstable under stressful conditions, such as pH, temperature, and mechanical stress but concluded that the therapeutic effect of HA-based preparations directly depends on the molecular weight and the concentration of HA in polymer solutions, which combined variables affect the stability of the HA molecule under stress (e.g., in the wound bed milieu). The researchers noted that HA solutions with molecular weights of 640 kDa and 1060 kDa maintained viscosity across the entire range of test frequencies. In addition, researchers noted that the surface tension of the HA molecule varied with concentrations ranging from 0.15% to 2.5% but that the recessions were small up to 2.5%.

The source of HA also makes a difference in the range of molecular weights of HA, which can be produced. HA from rooster combs has a high molecular weight of 1200 KDa. Furthermore, HA from rooster combs or other animal sources contains high levels of endotoxins and animal protein. Conversely, bacterial HA has a very low level of endotoxins, is devoid of animal protein, and with enzymatic techniques, enables HA production with a range of molecular weight between 550 kDa and 2500 kDa.

Evidently, the molecular weight of HA and the HA concentration in solutions leads to the reinforcement of the three-dimensional network of the polymer. The network results in an increase in HA solution viscosity and viscoelasticity. Conversely and practically, a reduction in viscosity would reduce stability, efficacy, and healing actions in the wound environment.

Investigation of a wound gel with molecular weight of 600 kda and 2.5% ha concentration

The investigated product characteristics include a 2.5% of HA concentration that was developed with a patented polymer matrix to maintain molecular and viscosity stability. The development purportedly evolved over a period of nearly 20 years. Problems included stability issues, revisions of manufacturing techniques, purity of raw materials, and the procurement of pharma-grade HA (not cosmetic grade). The HA in the product has a molecular weight of approximately 600,000 Daltons (600 KDAs).
In one of the first clinical studies regarding the product, the study’s objective was to ascertain if the wound gel, when placed on non-healing ulcers, would provide a more natural environment to aid ulcer healing. The study subjects included patients with one or more diabetic or non-diabetic venous stasis ulcers (n=50). A 1 mL of gel ratio was applied to 1 cm area of ulcer with a maximum daily dosage of 4 mL of gel per day. The duration of the 50 ulcers before study initiation ranged from 1 to 156.5 weeks, but in this study, the time to healing ranged from 1 to 24 weeks with a median healing time of 9.5 weeks (88% of ulcers were healed by study completion; P<0.05). Diabetic ulcers, however, had a median time to healing which was approximately 3 weeks longer than other types. Researchers concluded that the wound gel created an optimal environment for wound healing to occur.

In a second study regarding the subject wound gel, investigators conducted their research based on the theory that sodium hyaluronate has an important role in healing all stages of the wound, and their specific interest and focus was on the prospect of the gel’s efficacy in promoting varying types of difficult-to-heal lower leg and foot ulcers. One limitation of this study was the small sample size (n=20). At the study conclusion, the principal investigator was satisfied that more than 85% of the subjects had their wounds closed or improved after an average of 15 weekly wound gel treatments, and the investigator opined that regarding any wounds that did not close by the study end, those wounds improved so much that final wound closure was expected. Based on empirical, positive feedback from providers after this study was conducted in 2016, a wound care specialist could question if results from this 2016 study would have been even more robust if the wound gel had been applied more frequently than in just weekly intervals, such as daily.

In a third study of the subject wound gel (n=15), the surgeon-investigator provided background information that the healing of digit amputations is not often predictable, and its complications are an important cause of morbidity and mortality in patients with diabetes. The investigator also noted that digit amputations are common, multi-factorial, and costly complications in patients with diabetes. At study conclusion, Mayer concluded that the time to heal in those patients receiving HA gel daily after performing digit amputations was predominantly within 2 weeks, which contrasted with the typical 4-week healing time observed before using HA gel. In addition, the patient complication rate was correspondingly low because of the absence of incision line dehiscence or infection.

Literature review evidence in this paper may support the importance of diet in wound healing and the wound-healing benefits of specific dietary supplements for some patients. Research results also indicate that diet may affect the fusion or fission of mitochondria and that optimizing mitochondrial energy production can play a key role in wound healing. Scientific data and clinical data presented in this literature review may indicate that the specific potency and molecular weight properties of the subject HA formulation used in the present study may provide the logic and explanation for the unique efficacy of the formulation in refractory wounds, including refractory wounds with necrotic tissue. Because of the requisite brevity of this white paper, alternative views were not fully discussed. However, as a hyperbaric wound care specialist with over 20 years of clinical experience, we understand the nature of our profession and the differences in opinions resulting from clinical studies. We trust our observations and empirical results from treating patients facing amputations who experienced and benefited from refractory wound healing instead.

**CASE PRESENTATION**

All three patients received dietary consultation resulting in dietary supplementation of Vitamin C cofactor, hydrolyzed collagen peptides substrates, two dietary capsules containing a total of 7 mg L-methylfolate, 50 mg of pyridoxal5-phosphate, 2 mg of methylcobalamin, and 600 mg alaphalipoic acid,* and dietary removal of inflammatory gluten products, sugar, and dairy foods. Patients also received the application of a specialized wound gel product** at prescribed intervals to match dressing changes (e.g., BID, TID, titrated down to a few as 3 times per week). Patients also received individually prescribed HBOT.

**Case 1**

Thoracic surgeons Parsa et al., posited that the umbilicus is the body’s first scar and an important esthetic landmark of the abdomen, and procedures that change the shape or location of the umbilicus can result in an abnormal, bizarre, and esthetically displeasing abdomen, which often results in emotional distress. In some cases (e.g., an abnormally large hernia), the umbilical stalk arterial branches can be transected, resulting in damage to the umbilical vessels.

**Case 1 (dark purple umbilicus) description/results**

Her plastic surgeon referred a 42-year-old non-diabetic Hispanic female to the wound center following umbilical float abdominoplasty. Surgery was performed on November 7, 2022. On surgical follow-up (11/9/22), the umbilicus was noted to be dark purple with a slight incisional defect at 3 o’clock and had an odor and was then referred to the wound center for management.
The patient received dietary consultation. Vitamin C cofactor and hydrolyzed collagen peptides substrates were added to her diet, and inflammatory gluten products including sugar and dairy foods were removed from her diet. Topical natural polysaccharide substrate (i.e., specialized wound gel) was added to wounded area 2–3 times daily. The patient was also exposed to a hypertoxic environment (i.e., HBOT) at 2ATA with 100% O₂ ×90 min daily (20 treatments) to treat severe acute peripheral arterial insufficiency of the umbilicus. At 10 weeks, the wound was healed (Figure 1).

**Case 2 (dark purple umbilicus, contrasted therapy to Case 1) description/results**

Case 2’s outcome was initially vastly different from Case 1 because the treatment regimen only included HBOT. However, when dietary change and the wound gel were added to her treatment regimen at a different wound care center, her outcome was completely different, and favorable.

A 54-year-old Hispanic female presented for evaluation and treatment for a cavernous recalcitrant surgical wound (post-abdominoplasty performed on November 16, 2022). The patient presented with umbilical necrosis noted post-operative day 14 when bandages were removed, despite being treated at a different wound center with adjuvant HBOT ×2 weeks in December. After the 2-week course of HBOT, the patient was referred to a local emergency room by an outside wound center secondary to foul odor, a 6-cm deep hole with necrosis, fluid accumulation, abdominal swelling, and abdominal pain.

After a 3-day hospital stay, the patient stated that on January 5, 2023, she underwent wide excisional debridement and was started on negative pressure wound therapy in a local acute care facility. She refused recommended surgery and presented for the 1st time to our wound center on February 16, 2023, for treatment complications, including ischemic necrosis umbilicus following abdominoplasty. We implemented comprehensive wound care therapy, including...
wound gel, negative pressure wound therapy, and dietary intervention utilizing hydrolyzed collagen peptides, an alkaline diet, and adjuvant HBOT. In week 6, the patient achieved a >96% of reduction in both area and volume (Figure 2).

Case 3 (frontal foot with necrotic tissue)
A 69-year-old diabetic African-American male with Stage 4 chronic kidney disease reported sustaining a traumatic injury to the toes of his left foot while ambulating. He reported developing blood-filled blisters on all his digits. On November 7, 2022, the patient presented to the wound center emergently with necrotic digits ×5 of the left lower extremity foot. All toes were necrotic with dark purple discoloration and extended from the dorsum of all affected digits to the plantar and web spaces of the foot. The gangrene was wet with a pungent odor.

The patient stated that he normally cannot feel his foot but complained of discomfort. The patient was scheduled for emergent vascular consultation for the management of the suspected peripheral arterial disease. The patient underwent angioplasty with restoration of flow. The patient received dietary consultation and Vitamin C cofactor and hydrolyzed collagen peptides substrates were added to his diet.

**Figure 4:** Another results from Case 3

**Figure 5:** System model (prepared by Gossett K. with input from Payseur, S., Lesser, W., and Shashi, M.). This model reflected three measurable endpoints: (1) in vivo/clinical improvement in refractory wound healing parameters with the evidentiary restoration of necrotic tissue; (2) patient testimonials of treatment results; and (3) Health-care savings from avoided amputations were inferentially substantial. The HA wound gel is a FDA 510 (K) approved medical device product.
Inflammatory gluten products including sugar and dairy foods were removed from his diet. Topical natural polysaccharide substrate (i.e., specialized wound gel) was added to wounded area 3 times weekly. On November 30, 2022, the patient began daily exposure to a hyperoxic environment at 2ATA with 100% O₂ × 90 min daily treatments for limb salvage to multiple diabetic ulcerations complicated by tissue ischemia. By week 10, wounded toes ×4 were >90% resolved, and the 5th digit was >50% resolved at 10 weeks, with complete healing noted at 25 weeks, despite a hot-water-scalding setback during week 20 (Figures 3 and 4).

DISCUSSION

In this research study, a certified hyperbaric and wound care specialist evaluated in three patients, the effectiveness in healing of refractory wounds evidentiary with necrotic tissue in patients who were facing traumatic limb amputation or substantial tissue excision with reconstructive surgery using a novel, trifurcated treatment approach (after failed HBOT-only treatments). A system model (Figure 5) was created to explain the end-to-end process of research. The investigator determined that the successful wound closure and wound healing outcomes resulted from the trifurcated treatment approach, which treatment approach included: (1) Specific nutritional supplementation and diet alteration, (2) the application of a patented, high potency HA wound gel formulated with a specific HA molecular weight and a stabilizing, non-ionic polymer matrix, and (3) patient exposure to HBOT at prescribed intervals. All three patients experience wound healing and avoided extensive umbilical excision and reconstruction (Case 1 and Case 2) or limb amputation (Case 3).

Limitations of the study

Our study was done in a single hospital and so total number of the subjects were relatively small and this might affect the significance in our study result.

CONCLUSION

These results warrant further study with more subjects to determine the replicability of findings. If the results are generalizable to this population of patients who suffer from advanced refractory wounds and who are facing limb amputations, incalculable could be the health and quality-of-life benefits for these patients as well as the prospective cost savings on the U.S. health system.

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49.-element-1.png


51. Payseur, et al.: Treating refractory wounds with necrotic tissue
Payseur, et al.: Treating refractory wounds with necrotic tissue

Authors Contribution:
SP - Concept, design, implementation of study protocol, data collection, investigation; WL - Data collection, literature survey, manuscript writing, study model input; KG - study graphic model development, manuscript review/editing; MS - manuscript review/editing, article submission.

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