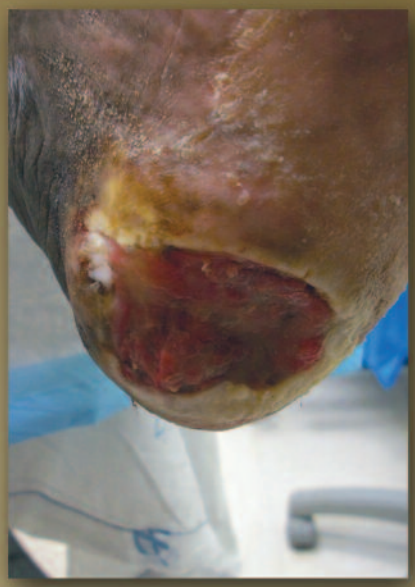
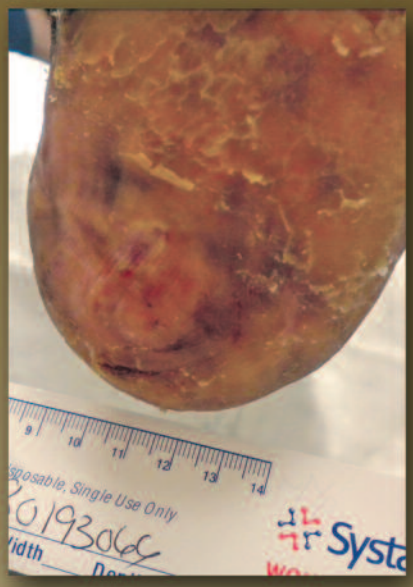


The ulcerated heel of an 84-year-old diabetic male.



The same wound, after eight weeks of treatment with integrated simultaneous therapy.

Integrated Simultaneous Regenerative Medicine: Revolutionizing the Treatment of Diabetic Foot Ulcers

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With the incidence of diabetes continuing to climb significantly among Americans, the need for a treatment protocol that consistently heals diabetic foot ulcers (DFUs) is pressing. Overall, DFUs are the single leading cause of limb loss in the US, with over 100,000 diabetes-related amputations performed annually.

At Winthrop-University Hospital's Wound Healing Center, every DFU patient is seen by a highly trained, interdisciplinary team, including specialists in diabetes, vascular surgery, interventional radiology, cardiology, podiatric surgery, general surgery, nephrology, emergency medicine and nutrition. What's more, nurses and physician assistants with advanced training in wound care, as well as a full-time attending physician, who serves as a "wound hospitalist," focus on the acute needs of hospitalized wound care patients 24/7. The team members' collaboration provides broad medical perspective on the treatment of persistent wounds while helping to manage common comorbidities, such as cardiovascular or kidney disease, which can impair the healing process significantly. Every effort is directed at preventing limb amputation.

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The deepest and largest DFUs are treated effectively **integrated simultaneous regenerative medicine.** An innovative approach, the technique combines a range of established evidence-based wound treatments — stem cell therapy, hyperbaric oxygen, growth factors, negative pressure therapy, highly precise debridement utilizing cellular markers and vascular surgery to improve blood flow — with careful management of each patient's underlying medical issues.

Leading-Edge Research

With growing understanding of the DFU healing process, a distinctive therapeutic model has emerged at Winthrop, where research — funded by three National Institutes of Health (NIH) grants from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) — has determined that the combination of diabetes and age produces biomolecular changes that directly impair the healing process. This explains why so many DFUs fail to heal.

The deficits include abnormalities in growth factors, cell function and restoration of the complex matrix of normal skin structure.[1] Additionally, it has been discovered that aging, alone, does not significantly impair healing. Rather, aging and diabetes together result in a 45% impairment of cellular response and healing,[2] accounting for the highest amputation rates in the elderly with diabetes.

While no single treatment modality is enough to overcome this impairment, the simultaneous use of all proven regenerative medicine modalities — including collagen, cellular growth factors, human cells, keratinocytes, stem cells and fibroblasts — combined with other treatment approaches, produces a synergistic effect capable of overcoming these physiological barriers to healing.

Regenerative Medicine Heals Diabetic Foot Ulcers

The integrated simultaneous therapy combines three forms of innovative regenerative medicine treatments that enable the regeneration of almost any tissue by promoting increased growth in areas where healing is physiologically impaired.

- **Cellular therapy** with graftskin (Apligraf®), which is the only drug that works on multi-

ple types of chronic wounds, is the current standard of care for refractory wounds.[3] Cellular therapy was recently shown to contain — in addition to the human keratinocytes and fibroblasts in Apligraf — endogenous epidermal stem cells that stimulate the healing of endogenous tissue.[4]

- **The topical application of growth factors** represents a major breakthrough in wound care. Platelet-derived growth factor-BB (PDGF-BB) and granulocyte macrophage colony-stimulating factor (GM-CSF) — both of which have been proven to promote angiogenesis and tissue growth in DFUs in clinical trials — are used. Other growth factors likely to be clinically available in the future include vascular endothelial growth factor (VEGF), which has been shown to stimulate growth of human fibroblasts and keratinocytes.[5] Furthermore, innovative time-release delivery systems are also under investigation.
- **Collagen-based therapies** are another important component of the wound-healing protocol.

To enhance results, wound care also utilizes the following modalities:

- **Hyperbaric oxygen therapy,** provided through the Hospital's nationally recognized Hyperbaric Medicine Program, promotes wound tissue oxygenation, which encourages blood vessel growth in the wound and improves the body's response to infection.
- **Negative pressure therapy** — VAC (vacuum assisted closure) therapy — utilizes a specialized sponge that stimulates granulation tissue and reduces bacterial colonization rates.
- **Surgical removal of infra-popliteal atherosclerotic plaque** from blood vessels in the lower leg restores and improves blood flow to the lower extremities, stimulating angiogenesis in areas where it was once considered impossible.

The Hospital's wound-healing protocol also includes weekly meetings with pathologists to review tissue pathology reports, which guide the type and timing of DFU treatment tailored to each patient. It has been established that areas around the edge of infected, non-healing wounds have characteristic abnormalities in tissue structure, protein expression and gene activity — abnormalities that clearly demonstrate an intrinsic healing defect. When the rim of healing-impaired tissue is removed from the edge of a chronic wound, the cellular healing process can begin. What's more, important biomolecular markers that distinguish healthy tissue from impaired wound tissue unable to heal have been identified. Most notably, the c-myc gene, which is involved in cell differentiation, is abnormally expressed in non-healing wound tissue.[6]

The underlying pathology (i.e., fibrosis, infection, ischemia, viable bone, etc.) of the post-debridement tissue provides an objective basis to guide subsequent treatments, including further surgical debridement, regenerative medicine and reconstruction. As a result, treatment modalities have become more precise, reducing the number of debridement procedures. Most important, these techniques have resulted in a significant decrease in limb loss.

The use of these therapies in combination and simultaneously is unusual. At Winthrop, it is the standard of care. Individually, none of these treatments is likely to overcome the underlying DFU patients' physiological impairments, but used together, they have consistently regenerated healthy tissue in refractory DFUs.[7]

For more information about Winthrop's Institute for Heart Care call 1-866-WINTHROP or visit www.winthrop.org..

Case Study

A retired, 80-year-old pilot and avid tennis player with Type II diabetes was treated unsuccessfully for an ulcer on his toe, which had turned gangrenous. Told that he needed a limb amputation, he turned to our team for help. He was admitted immediately and quickly examined by a wound physician, cardiologist, vascular surgeon and nephrologist. Comorbidities included electrolyte imbalance, difficult-to-control diabetes and cardiac failure.

After hydration and cardiac optimization, the patient underwent debridement, with collagen and GM-CSF applied to his wound. Soon thereafter, an arterial bypass in his lower leg was performed to remove a blockage. Days later, after a second debridement, cellular therapy was administered in addition to collagen and GM-CSF. He was also given an intravenous broad-spectrum antibiotic to combat infection, which had spread to the bone. Following the second procedure, his pain decreased significantly, and he was no longer at risk for amputation.

After discharge, the patient received ongoing outpatient therapy, including IV antibiotics. He continued to be closely monitored, receiving additional debridement, hyperbaric oxygen, cell therapy and a skin graft. Subsequently his wound closed, and he was back on the tennis court.

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