Treatment of Venous Ulcers With Human Skin Equivalent

To the Editor:

Because ulcerations are the most frequently occurring chronic wounds of the lower extremity, the podiatric physician can play an important role in the evaluation and implementation of new ulcer-healing technologies.[1] The cause of many lower limb ulcers encountered by podiatric physicians is likely to be venous disease. In a recent Australian study, the prevalence of chronic ulceration of the leg was found to be 1.1 per 1,000 population; venous insufficiency was determined to be the sole cause or a contributory factor in 67% of these ulcers.[2]

Venous ulcers are most prevalent in older patients; approximately 10 per 1,000 patients 80 years of age and older have chronic ulceration associated with venous disease.[2] Thus, the likelihood of encountering patients with venous ulcers will increase as the population ages.

Venous ulcers are frequently chronic, recurrent, and difficult to treat. Many types of treatments have been used in attempts to heal these ulcers, including various compressive devices, dressings, and topical medications.[3] A recent review of the literature indicates that a combination of a dressing with a compression bandage, as provided by the Unna boot, is the most effective treatment currently available for these ulcers.[4] Although compression therapy is an important component of treatment, one study revealed that only 14% of ulcerated limbs were treated by appropriate compression.[5, 6] The low proportion of patients effectively treated by compression therapy may stem from incorrect application of the therapy or decreased patient compliance owing to the large time and labor commitment that the treatment requires. Autologous skin grafting also promotes healing of ulcers, but it is an invasive, expensive, surgical procedure requiring inducing anesthesia and the removal of skin from a donor site.[8, 9] In most states, such surgical procedures are outside the scope of practice of podiatric physicians.[10] An effective, inexpensive, easily used therapy for venous ulcers is needed.

Experience With Human Skin Equivalent

While at the California College of Podiatric Medicine in San Francisco, the author participated in a large, multicenter study examining Apligraf®[1] human skin equivalent, a cultured human allograft, to promote wound repair in venous ulcers.[11] This material was previously shown to be effective in healing acute surgical wounds and is currently being assessed in other wounds such as diabetic and pressure ulcers and burns.[12] Human skin equivalent, which consists of living dermal and epidermal layers grown from human neonatal foreskin cells, resembles human skin on both gross and histologic levels (Fig. 1). Because the skin material is nonimmunogenic, it can be safely grafted in humans with no signs of immunologic sensitization. The material is expanded in culture from cells derived from a single donor and is routinely tested to establish that it is free of adventitious pathogens such as the human immunodeficiency virus.[12]

Human skin equivalent was found to be easy to apply in an outpatient setting. The allograft was simply placed on the wound and then trimmed with scissors to fit. It was then covered by a nonadherent primary dressing followed by a secondary nonocclusive dressing (cotton gauze) folded as a bolster and a self-adherent elastic wrap to hold it in place.[11] The proportion of patients with wound closure by 6 months was 61.4% *versus* 44.3% for compression therapy (P = 0.012).[11] More rapid healing was also observed in the human skin equivalent group compared with that in

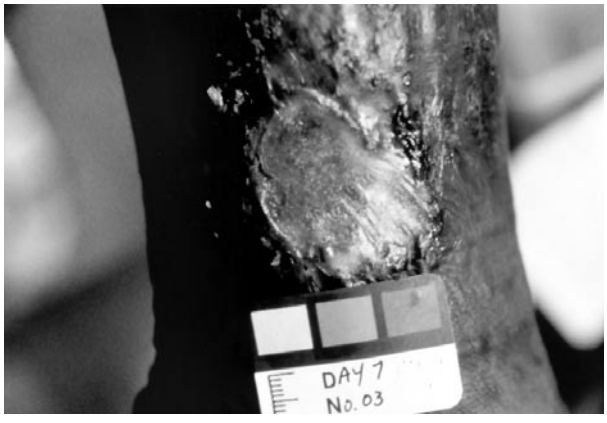

Figure 1. Human skin equivalent positioned on a chronic venous ulcer.

®[1] Organogenesis, Canton, MA.

the compression therapy group. The median time to wound closure was 57 days for human skin equivalent-treated patients *versus* 181 days for compression therapy-treated patients (P = 0.0066).[11]

Adverse event occurrences were similar between the human skin equivalent and compression therapy groups. Human skin equivalent therapy did not result in any problematic side effects. No laboratory or clinical evidence of allograft rejection was observed (V. Falanga, MD, unpublished data, February 1997).

The quality of wound healing provided by human skin equivalent was high; the resulting tissue appeared to be more resilient than that observed following compression therapy.[11] Figure 2 shows a characteristic venous ulcer wound before the application of human skin equivalent and after human skin equivalent-mediated healing. Patients were generally pleased with the appearance of the material, and many expressed great satisfaction in seeing their wounds closed for the first time in years.

In addition to the favorable clinical attributes of human skin equivalent, it may be more cost-effective than compression therapy alone when ease of application, efficacy, and reduction in the number of visits required with this agent are taken into account. A recent study of leg-ulcer management methods determined that the greatest economic savings were realized by methods that most improved healing.[13] Since human skin equivalent has been shown to be more effective than the Unna boot, which is currently the most effective therapy for venous ulcers, it may become an important, cost-effective treatment for this condition.

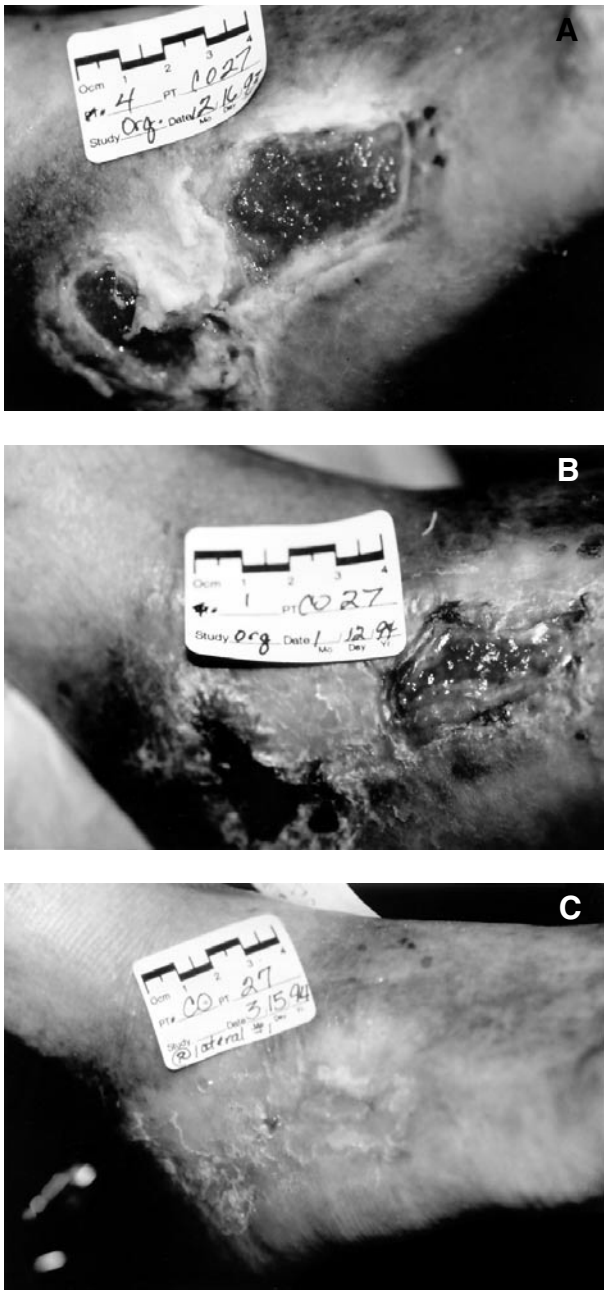

Figure 2. Human skin equivalent-mediated healing of a chronic venous ulcer. A, Untreated ulcer. B, Wound appearance 4 weeks after application of human skin equivalent. C, Three months after human skin equivalent application, the ulcer is healed.

Summary

In the author's clinical experience in rating venous ulcers, human skin equivalent has been efficacious, safe, cost-effective, and easy to use. This innovation is likely to become an important therapeutic tool for podiatric physicians who treat venous ulcers. Leg ulcers are a large economic burden to society, both in direct and total costs, including patient time lost from work for labor- and time-intensive therapies.[14] The cost-containing measures of the managed care environment encourage treatment of venous ulcers in an outpatient center. Because human skin equivalent can be applied in such a setting, podiatric physicians will be able to treat venous ulcers routinely without referring patients to more costly settings such as hospitals or surgical centers. Because human skin equivalent is an effective alternative to standard venous ulcer therapies, this agent, which is currently under review by the Food and Drug Administration, should provide a viable treatment that may reduce the total costs associated with venous ulcer care.

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Gout and Hypothyroidism

To the Editor:

Studies have shown an association between gouty arthritis and hypothyroidism.[1-4] In 1955, Kuzell et al[4] reported that in 504 patients with gout, 18.7% of the men and 29.7% of the women with gout also had hypothyroidism. Leeper et al[2] reported hyperuricemia in 11 of 12 men and six of 16 women in a 28-patient study of patients with myxedema. They also were able to increase the uric acid excretion in these patients an average of 2.0 mg/dl by normalizing thyroxine levels with triiodothyroxine. Most recently, Erickson et al[1] studied the prevalence of hypothyroidism in 25 patients with gout. They found a correlation ($p < 0.05$) of hypothyroidism in females (25%) and males (12%) with acute gouty arthritis when compared with controls. These patients had noninflammatory arthritic conditions and were the same age, weight, sex, and race.[1] Nordstrom and Merenich[3] performed a statistical study that seemed to confirm the findings of these three previous studies, and concluded that hypothyroidism is probably not a cause of hyperuricemia but a precipitating factor in those who are predisposed to the condition. They base this on elevated urate excretion rates after the administration of thyroxine. The investigations by Dumitriu et al[5] of hypothyroid patients showed that an excess of adenosine diphosphate occurs in hypothyroid patients which degenerates into the substrate xanthine during lipid peroxidation. These greater levels of xanthine lead to increased serum uric acid levels.[5, 6] The research by Trokoudes et al[7] research on thyroid-stimulating hormone receptors in extrathyroidal tissues (adrenal and testicular) led Erickson et al[1] to hypothesize that thyroid-stimulating hormone receptors may also occur in the kidney and possibly control urate metabolism. Table 1 reviews the etiologies of secondary hyperuricemia, and Table 2 reviews the systemic effects of hypothyroidism.

Case Report

A 35-year-old male presented to Foot Clinic of New York with the chief complaint of sudden onset of throbbing pain in the right big toe, of 4 days' duration. The pain began the day after an exercise session that included jumping rope. He was on a high-protein, low-carbohydrate diet for 1 week in an effort to lose weight. The patient attempted ineffectve self-treatment by applying ice to the affected area and taking six aspirin for pain. The patient was taking no other medications and the remainder of his medical and surgical histories was unremarkable. The patient's father had a history of gout which began at 40 years of age, expressing three subsequent attacks during 20 years.

The physical examination revealed a six-foot, 248-pound male. Blood pressure was 130/90, pulse 72, and respiration 16. Vascular, neurologic, and muscle power examinations were normal. The orthopedic examination demonstrated limited and painful range of motion of the right first metarsophalangeal joint. The area was warm, erythematous, and tender to palpation. Blood analysis and urinalysis revealed white blood counts of 11.6 c/mm^3, polyPMN's of 80.1%, lymphocytes of 12.2%, monocytes of 5.7%, eosinophils of

Table 1. Etiologies of Secondary Hyperuricemia

Urate Over-production	Decreased Urate Excretion
Glycogen storage disease types 1, 3, 5, 7	Chronic renal disease
Tissue hypoxia	Dehydration
Increased ethanol intake	Diabetes insipidus
Metabolic myopathy	Starvation
Blood dyscrasias	Diabetic ketoacidosis
Malignancies	Acute ethanol ingestion
Psoriasis	Lead poisoning
Excessive purine intake	Hypothyroidism and other endocrine disease
Infectious mononucleosis	Toxemia of pregnancy
Lesch-Nyhan syndrome	
Chemotherapy	Medications
	Cyclosporine
	Pyrazinamide
Undetermined Causes	Salicylates (low doses)
Sickle cell disease	Ethambutol
Lead nephropathy	Nicotinic acid
Polycystic kidney disease	Diuretics

Table 2. Review of Possible Systemic Effects in Hypothyroidism

Integument and Appendages
Pale, cool, puffy skin. Dry, brittle hair and nails. Carotenemia. Nonpitting edema.

Eyes, Facial Appearance
Periorbital edema, loss upper third of eyebrows; puffy facial features; macroglossia.

Cardiovascular System
Bradycardia: decreased peripheral vascular resistence, heart rate, stroke volume, cardiac output and pulse pressure

Respiratory System
Hypoventilation, CO_2 retention.

Gastrointestinal System
Decrease in appetite, constipation.

Central Nervous System
Lethargy, slow mental processes, peripheral neuropathy.

Musculoskeletal System
Fatigue, stiffness with decreased deep tendon reflexes. Increased alkaline phosphatase, lactate dehydrogenase, serum glutamic-oxaloacetic transaminase.

Renal System
Decreased renal excretion, glomerular filtration rate.

Hematopoietic System
Anemia: normocytic, microcytic, or macrocytic. Hyperchromic or hypochromic. Decreased iron absorbtion, folate, or autoimmune pernicious anemia.

Reproductive System
Menorrhagia, infertility, decreased libido, impotence, decreased gonad and steroid metabolism.

Metabolic System
Decreased basal metabolic rate; positive nitrogen balance, delayed insulin degradation and increased insulin sensitivity; increased cholesterol and triglycerides; decreased drug detoxification.

1.6%, and basophils of 0.4%. Serum uric acid of 7.3 mg/dl was mildly elevated. Serum iron was 40 mcg/dl. The transferrin iron binding capacity was 271 mcg/dl. HDL was 32 mg/dl and triglycerides were 231 mg/dl. The urine was cloudy, yellow with trace bilirubin and uric acid crystals were variable. A presumptive diagnosis of acute gout was made based on family history, clinical presentation, and serum urate levels. Treatment consisted of a 1% Xylocaine block at the level of the right first metatarsophalangeal joint to alleviate ambulatory pain. Indomethacin, 50 mg three times a day, was prescribed for 7 days. The patient was referred to his primary physician for management of the hyperuricemia.

Joint pain and limited range of motion persisted when the patient presented to his family physician 1 month later. The patient also demonstrated complaints of lethargy, mental sluggishness, and an inability to lose weight. The patient had no goiter or palpable nodes. Blood analyses at that time revealed serum uric acid 8.6 mg/dl, a transferrin saturation of 54% with normal serum iron of 151 mcg/dl, and a transferrin iron binding capacity of 280 ug/dl. Triglycerides were 234 mg/dl, and cholesterol was 159 mg/dl. Serum lactate dehydrogenase was increased to 648 U/liter.

A thyroid-stimulating hormone assay was performed, based on the patient's clinical complaint and presentation. The patient's thyroid-stimulating hormone level was 15.65 mU/liter (normal range is 0.05-5.0 mU/liter).[8] An elevated thyroid-stimulating hormone level above 5.0 mU/liter is diagnostic for primary hypothyroidism.[9] The thyroid-stimulating hormone level was reevaluated 1 week later and was 18 mU/ml. The patient was prescribed levothyroxine 150 mcg every day. After waiting 6 weeks to achieve thyroxine blood levels, the patient's thyroid-stimulating hormone level normalized to 1.7 mU/liter. Triiodothyronine uptake was 31.0 %, tetraiodothyronine (T_4) radio immunoassay measured 9.0 ug/dl, and the free thyroxine index was 2.82 free thyroxine index units, which were all normal values.[8] The patient has not reported a subsequent gouty attack since beginning treatment with levothyroxine.

Summary

A case of gout in a patient with primary hypothyroidism has been presented. Often missed as a companion of gout, hypothyroidism has a frequency of occurrence with gout that is significant and is probably a precipitating factor in these gouty attacks. The physician should be alert for signs and symptoms of this often occult disease in patients with hyperuricemia and gout.

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