Healing of Elderly Patients with Diabetic Foot Ulcers, Venous Stasis Ulcers, and Pressure Ulcers

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ABSTRACT

Although elderly patients have physiologic impairments in wound healing, their wounds should be expected to heal with the same frequency of closure as those in younger populations, albeit at a slower rate. However, compared to the general population, the elderly population has a higher incidence of chronic wounds: diabetic foot ulcers, pressure ulcers, and venous stasis ulcers. Experimental and clinical data indicate

physiologically impaired healing is characterized by decreased angiogenesis and synthesis of critical growth factors. Further, compared to younger populations, the elderly have a higher rate of mortality associated with specific morbidities, such as sepsis and acute respiratory distress. As these morbidities may develop directly from the wound, early intervention is mandated. In this report, 40 consecutive elderly patients (65-102 years old) with chronic wounds were analyzed. All patients were provided the same treatment protocol and healing was defined as 100% epithelization and no drainage. Despite the wounds presenting in a nonhealing and/or infected state, 73% of these chronic wounds in elderly patients healed. This suggests that elderly patients with diabetic foot ulcers, pressure ulcers, and venous stasis ulcers close their wounds at a similar frequency as younger patients. Therefore, early intervention and comprehensive treatment that includes safe topical therapies, in addition to growth factors and cellular therapy used for chronic wounds, ensure these patients will be spared the morbidities of pain, amputation, osteomyelitis, and even death. We hypothesize that if all elderly patients with chronic wounds are provided early treatment, morbidities (e.g., amputation, sepsis, pain) and associated costs will decrease.

INTRODUCTION

Acute wounds heal sequentially and in a timely manner with overall restoration of anatomic and functional integrity. Chronic wounds, however, are characterized by underlying physiological impairment that prevents normal restoration of anatomic and functional integrity, unless adequate intervention is provided.[1-3] A common misconception is that a wound needs to be present for an extended period of time before it can be designated as "chronic;" chronic wounds are not time dependent, and treatment should be provided immediately upon recognition. As soon as a patient develops a diabetic foot ulcer, a venous stasis ulcer, or a pressure ulcer, they mandate immediate treatment, regardless of age. However, the elderly suffer the greatest morbidities when treatment is not initiated immediately.

Chronic wounds (e.g., diabetic foot ulcers, venous stasis ulcers, and pressure ulcers) are experienced commonly in the elderly population,[4-8] leading to another misconception, that elderly patients cannot heal simply because of advanced age, although the higher rates of chronic wounds experienced by elderly patients cannot be attributed to advanced age alone. Rather, the combination of advanced age and a high incidence of other morbidities associated with advanced age—such as diabetes, chronic venous insufficiency, and immobility—results in the high rates of diabetic foot ulcers, venous stasis ulcers, and pressure ulcers in this population.

The purpose of this report is to discuss the conducted experimental and clinical studies that investigate the effects of aging on the wound-healing process. Also, data that demonstrate chronic wounds in elderly patients can be expected to heal are reported.

WOUND HEALING AND AGING

To interpret experimental and clinical data from wound-healing studies that relate to the elderly, one must understand the concept of life expectancy, because it is the basis for defining the term "elderly population." According to the National Center for Health Statistics, life expectancy is defined as "the average number of years of life remaining to a person at a particular age" and "may be determined by race, sex, or other characteristics using age-specific death rates for the population with that characteristic."[9] According to the Center for Disease Control, life expectancy for the human population at birth is 74.1 years for men and 79.5 years for women.[10]

Multiple animal models are available for studying the wound-healing process and its variation with age, many from the National Institute of Aging.[11] For example, aging studies on wound healing have compared young to old murine models (young mice: 2-8 months; old mice: 22-27 months),[12-14] rat models (young: 1-4 months; old: 1-3 years),[15-18] and rabbit models (young: 4-8 months; old: 4-5 years),[12,18] as well as many others. In particular, animal models have been used to investigate, in detail, the effect of aging on a process critical to wound healing—angiogenesis.

ANGIOGENESIS AND WOUND HEALING

Angiogenesis, or the regulated growth of new blood vessels,[19] depends on the interplay of cells, soluble factors, and extracellular matrix (ECM) components.[20] Angiogenesis is vital to wound healing,[21,22] because it provides the wound with a network of blood vessels that allow macrophages and other critical cells, many of which synthesize angiogenic growth factors to infiltrate the wound and accelerate healing. More than 30 regulatory mechanisms of angiogenesis have been observed in a wound, including growth factors, their receptors, matrix metalloproteinases (MMPs), and chemotactic agents. As an example, the mitogenic effect of some of the growth factors synthesized in a wound regulate and stimulate endothelial cells to migrate into the wound and new capil-

laries to form. Furthermore, angiogenesis also is stimulated in wounds by enzymes such as MMPs, which degrade most ECM components, a process essential to newly forming blood vessels.[23] Since angiogenesis requires many steps, it is essential to specify the details of which step is impaired in a particular wound (i.e., in the wound of an elderly patient). Reversal of that one particular impairment, and a subsequent outcome of accelerated healing, indicate the mechanism in question as critical to the angiogenic process, and therefore, to the wound-healing process.

EXPERIMENTAL EVIDENCE OF IMPAIRED ANGIOGENESIS WITH ADVANCED AGE

Impairment of angiogenesis prevents wounds from healing in an orderly and timely manner,[21,22,24] and this impairment correlates with advanced age. For example, capillary density is reduced significantly in wound specimens in multiple-aged experimental models.[12,13,17]

Another significant indicator of decreased angiogenesis in a wound is impairment of macrophages, cells critical in the healing response. Macrophages are among the first cells to infiltrate the wound and secrete a number of important growth factors into the wound,[25] such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). Decreased macrophage function is one established critical mechanism of delayed healing in an experimental model of wound healing and aging.[14] This impairment of macrophages is further exemplified by the significantly accelerated healing that results from injecting macrophages obtained from young mice into aged mice (24-27 months); macrophages from younger donors (5-8 months) proved more effective than those obtained from older donors (24-27 months) in accelerating healing in old recipients (24-27 months).[26] A reduction in the amount of specific angiogenic factors released also is observed in addition to decreased macrophage function correlated with advanced age. Aged mice (22-24 months) have a 50% greater reduction in VEGF levels compared to young mice at day 5 post-wounding; they also demonstrate a significant reduction in bFGF levels.[13] Furthermore, aged ischemic rabbits (4-5 years) also have a significant reduction in growth factor expression: VEGF expression is decreased in smooth muscle cells obtained from old specimens in hypoxic conditions.[18]

CLINICAL EVIDENCE OF IMPAIRED WOUND HEALING IN THE ELDERLY

Clinical studies in the past have suggested impairment in the wound-healing process of the elderly. For example, in a study from 35 years ago, an increase was observed in post-surgical dehiscence rates in elderly patients (i.e., 83% were aged 60 years or older[27]). The incidence of post-surgical dehiscence increased by as much as three times for patients over the age of 60 years, compared to younger patients.[28] In addition, elderly patients (>65 years of age) showed decreased rates of healing compared to younger patients (18-50 years of age) when superficial, split-thickness, 2-×2-cm wounds were created on the anterior aspect of the thigh. Specifically, elderly participants demonstrated delayed epithelialization, as measured by the difference in total alpha-nitrogen content in polytetrafluoroethylene (PTFE) catheters, a reflection of total protein accumulation. The values were significantly higher in the younger group (38.9 ± 3.22 vs. 21.95 ± 2.49 µg/cm).[29]

In another clinical example, the effect of age on the capacity of human skin to mount an inflammatory response was examined by comparing sunburn reactions quantitatively in two groups of subjects. The first was 22-26 years of age and the second, 62-86 years of age. Skin taken from the buttock of each subject was exposed to ultraviolet light. Non-irradiated skin of older adults contained approximately 50% less histamine and prostaglandin E_2 (PGE_2) than that of young adults. Histamine level 4-hour peak values averaged 9.2 ng/mL in elderly subjects compared with 18.3 ng/mL in young subjects. At 4 and 24 hours post-irradiation, elderly patients also demonstrated impaired mast cell and endothelial cell response. The data suggested that, with advancing age, the sunburn reaction is quantitatively reduced and evolves more slowly following a standardized ultraviolet exposure.[30] Thus, this study suggested an impaired inflammatory response in the elderly.

One possible mechanism of impaired wound healing in the elderly may be that critical growth factors released by platelets, such as insulin-like growth factor (ILGF), are decreased in the postoperative period.[31] This process is critical because the release of other growth factors, such as VEGF, may depend on ILGF release from platelets. Thus, a deficiency in one growth factor may result in the decreased levels of other growth factors in a wound.

Although healing may be impaired in elderly patients, the impairments should not deter immediate treatment, especially because chronic wounds have several associated complications to which elderly patients are more likely to succumb (e.g., amputations, sepsis, or osteomyelitis). This correlation is evident by the overall increased incidence of morbidities and mortality in older age groups. In a study that involved 847 hospitals and 192,980 patients, the incidence and outcome of severe sepsis were quantified. Results showed that the incidence of sepsis increased 100-fold with age (.2/1,000 in children to 26.2/1,000 in those >85 years of age). Further, the mortality rate from sepsis also was significantly age-dependent; it increased from 10% in children to 38.4% in those older than 85 years.[32]

Respiratory impairment in the elderly is another clinical example of which the elderly have less ability to cope with significant disease. Patients with acute respiratory distress also have significantly higher mortality rates (64%) when their age is greater than 55 years, compared to mortality rates in those 55 years and younger (45%).[33] In a retrospective study that reviewed age-related outcomes after major non-cardiac surgery, a greater risk was reported in older patients for developing pneumonia postoperatively. Specifically, compared to patients younger than 50 years old, patients aged 70-79 years had an odds ratio of 3.58, and those 80 years and older had an odds ratio of 5.63 for developing pneumonia.[33]

INCREASED INCIDENCE OF CHRONIC WOUNDS IN THE ELDERLY

Healing impairments correlated with advanced age, along with the increased incidence of diabetes, venous insufficiency, and immobility in the elderly population, together contribute to the increased rates of diabetic foot ulcers, venous stasis ulcers, and pressure ulcers, characteristic of this population.

Diabetic Foot Ulcers

The prevalence of diabetes in the United States has increased significantly over the years, from 5.8 million persons

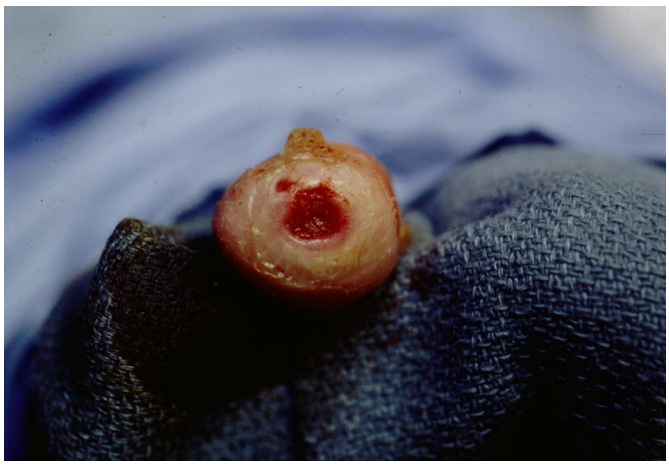

Figure 1a. Toe ulcer of a 70-year-old man with type-2 diabetes, first seen with an infected cellulitic toe ulcer. This figure depicts the wound after intravenous antibiotics and surgical debridement.

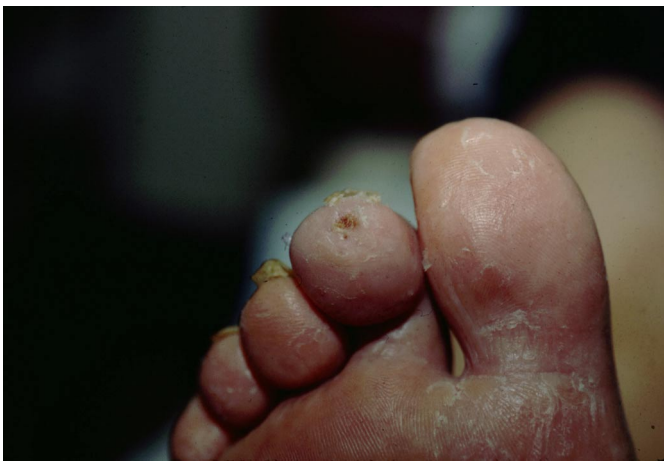

Figure 1b. Patient's toe ulcer healed after early comprehensive treatment. There should never be an exception to proper wound-bed preparation (i.e., early surgical debridement in a diabetic foot ulcer and treatment with antibiotics targeted directly toward bacteria growing from the deep culture) because a patient is elderly. The elderly can heal if provided with early intervention and comprehensive care.

diagnosed in 1980 to a total prevalence estimated at a minimum of 12.1 million in the year 2002.[34] This increase especially relates to the elderly population (Fig. 1). Generally, people aged 65-74 years had the highest prevalence of diabetes, followed by those aged 75 or older. In addition, in 1999, the prevalence of diagnosed diabetes among persons aged 65-74 (14.51 per 100 population) was more than 13 times that of those younger than 45 years of age (1.10 per 100 population).[35] Diabetic foot ulcers, a major complication associated with diabetes, are present in 15% of all patients who suffer from the disease.[36] Therefore, one can expect a higher prevalence of diabetic foot ulcers in elderly patients with diabetes, in particular, because of the increased incidence of diabetes in this population, based on the above statistics. Supporting this expectation, rates of hospital discharges for non-traumatic, lower-extremity amputations—a serious comorbidity of diabetic foot ulcers—are higher in elderly patients with diabetes as compared to younger patients with diabetes. Specifically, the rates (per 10,000 population) were 1.5 for patients less than 65 years of age, 12.7 for patients 65-74 years old, and 17.4 among the elderly more than 74 years.[35]

Experimentally, it is well-established that a significant impairment exists in the production of angiogenic growth factors from the fibroblasts in wounds when diabetes is present.[37] Therefore, we hypothesize that the combination of age and diabetes accounts for the significantly delayed healing and increased amputation rate in the elderly. The amputation rates in patients with diabetes who develop heel ulcers are significantly high. Thus, the urgency is to treat these ulcers as soon as they are noticed, before they progress and become difficult to heal, and before morbid complications develop.

Venous Stasis Ulcers

Advanced age has been implicated as a risk factor for increased severity of venous insufficiency.[38] Concurrently, the prevalence of venous ulceration also increases progressively with age;[39,40] 90% of patients with venous ulceration are 60 years and older.[41] As a consequence of a higher incidence and greater severity of chronic venous insufficiency, venous stasis ulcers are more common in the elderly than in other age groups. It is likely that age impairs the valves that result in venous reflux. We maintain that it is venous reflux and its sequelae that primarily may impair healing, and not age alone.

Pressure Ulcers

Lack of mobility in the elderly greatly contributes to a high percentage of pressure ulcers in this population.[42] At one year post-discharge, elderly patients who develop hospital-acquired pressure ulcers have higher mortality rates than those who do not.[43] A national hospital study reported that 73% of patients who developed hospital-acquired pressure ulcers were 65 years or older.[44] The data confirm that pressure ulcers are a severe problem in the elderly population, but do not confirm age itself is a variable that increases the incidence of pressure ulcers.

CLINICAL EXPERIENCE

In our clinical experience, early intervention—including debridement of chronic wounds—is sometimes delayed in the elderly, perhaps because of inferences drawn by healthcare providers from experimental evidence that suggests the elderly cannot heal. This delay is evidenced by the observation of hundreds of elderly patients treated under the care of our team, whose wounds clearly had not been provided early treatment. By the time these patients came to our wound-care center, the wounds often had worsened dramatically.

In nearly every treatment milieu, one characteristic has almost always been present. The elderly patient's wound is allowed to progress because other morbidities suffered by the patient are more readily recognized and treated. For example, we have treated hundreds of patients with sacral pressure ulcers and heel ulcers that have progressed to Stage IV because the main focus of treatment of the patient was another disease. This problem is most prominent in spinal cord injury patients, those with respiratory or renal failure, nursing-home patients recovering from a series of medical illnesses, bed-bound patients being treated by

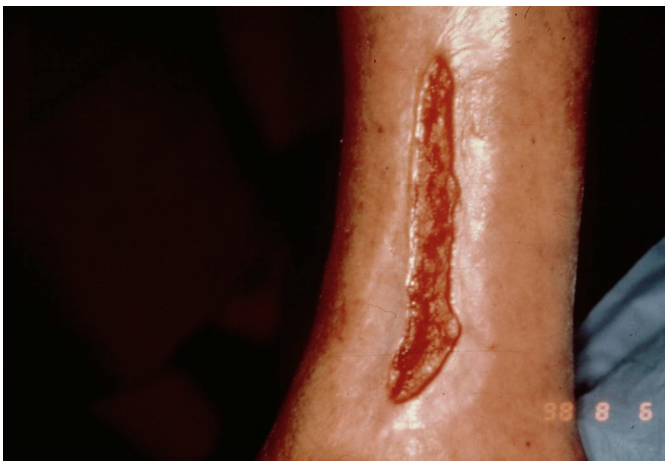

Figure 2a. 82-year-old patient with diabetes first seen with a venous stasis ulcer of an 18-month duration that started after a vein was harvested for coronary arterial bypass grafting. Costs for daily nursing visits regarding this patient's wound treatment alone totaled over $70,000. Doppler ultrasound confirmed venous reflux. No data exist that patients with diabetes and venous reflux have a different rate of healing.

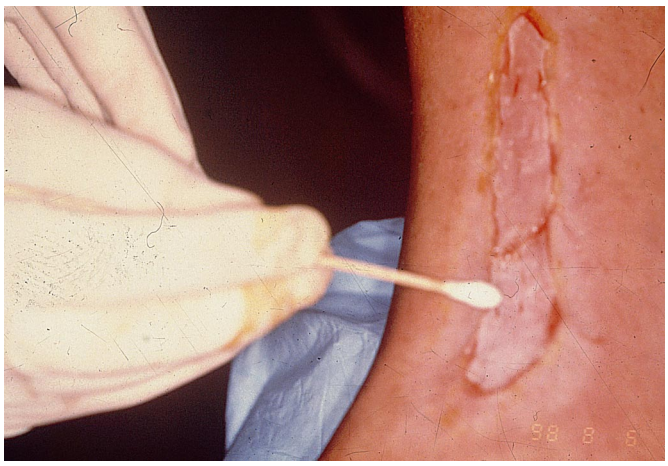

Figure 2b. Note bilayered human skin equivalent (HSE) (cultured keratinocytes and fibroblasts on type-1 collagen) being applied to the venous ulcer. Application was administered in an office setting with a 1-mm distance left between debrided healing skin edge and new bilayered HSE.

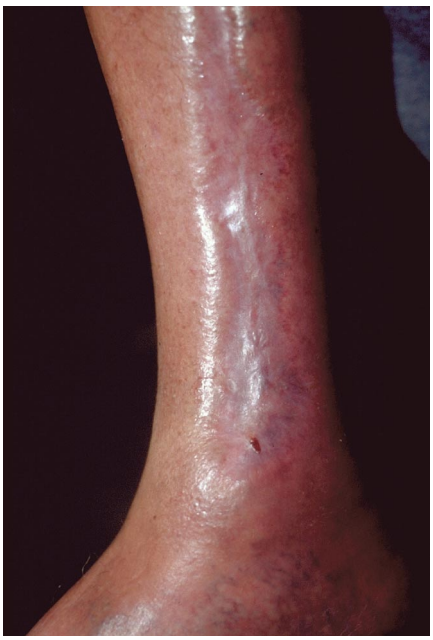

Figure 2c. Venous stasis ulcer healed at 7 weeks.

home-care physicians and nurses, and intensive care unit patients. However, the potentially grave complications associated with chronic wounds in the elderly make it imperative to determine the best combination of therapies that prevent these wounds from progressing further, as well as accelerate healing. We propose that regular use of established surgical and wound healing techniques—in conjunction with all available treatments—will result in complete healing of chronic wounds in the elderly at similar frequency of closure as compared to younger patients.

Forty consecutive patients who received the same treatment protocol were retrospectively analyzed for frequency of wound closure. The standards of wound care applied during treatment included offloading pressure ulcers and diabetic foot ulcers, surgical debridement of all non-viable tissue, and compression for venous stasis ulcers. In addition, bilayered living HSE,[3,45-50] consisting of cultured keratinocytes and fibroblasts on Type I collagen, was applied to all wounds in this study.

METHODS

Treatment was administered to 40 consecutive patients between 65 and 102 years of age with one or more non-healing venous stasis ulcers, diabetic foot ulcers, or pressure ulcers (sacral, trochanteric, or ischial). Each wound was between 1 cm and 15 cm in length. After surgical debridement, bilayered living HSE was applied to each patient, leaving approximately 1 mm between the new skin edge and bilayered HSE. The grafts were applied in a sterile environment in either the office or operating room. All patients received antibiotics if they had cellulitis or drainage.

RESULTS

Overall, 29 of the 40 elderly patients experienced 100% healing within 6 months (see Figs. 1 & 2). One patient, an 82-year-old man, with diabetes and venous reflux, had a venous stasis ulcer of an 18-month duration. Bilayered HSE was applied to the wound, and the patient experienced complete healing in 7 weeks (see Fig. 2). The wounds of the 11 patients who did not heal to 100% either extended to the bone, or showed a deep soft-tissue infection such as methicillin-resistant *Staphylococcus aureus*. Those wounds that did not heal were generally allowed to progress into a refractory state before presentation. Nearly all of these that did not heal improved significantly (Fig. 3).

After adequate surgical debridement, all wounds should be expected to begin the healing process. We emphasize that debridement is needed to remove non-viable tissue and stimulate healing. In every surgical debridement, every wound has filled in with granulation tissue. Furthermore, in the our series, patients required no more than three debridements before bilayered living HSE application. Debriding any wound to the level in which scar tissue and infection are no longer present is safe and therapeutic in the elderly (see Figs. 1-3).

CONCLUSION

Initial recognition of ulcers in the elderly should prompt an immediate visit with the patient's physician to prevent progression of pressure ulcers to Stage IV, cellulitis and pain, non-healing venous

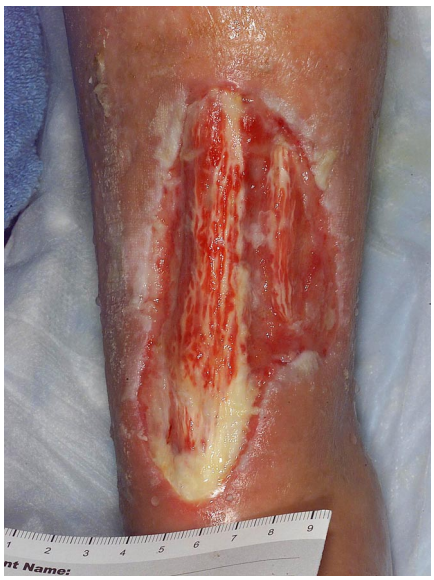

Figure 3a. This 84-year-old female patient presented after her wound had progressed and she had completely stopped ambulating because of the ulcer. The wound depicted is before operative debridement. Note non-viable tissue in inferior edge. Deep culture showed *pseudomonas*. Patient received one month of home intravenous antibiotics, and was surgically debrided (note significant portion of tendon was debrided in longitudinal fashion and ambulation was improved). Patient received bilayered human skin equivalent (HSE); however, compression therapy could not be placed for venous reflux because arterial brachial index was 0.41.

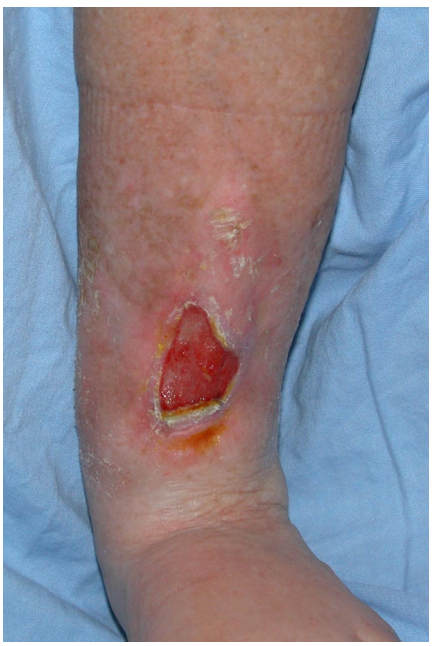

Figure 3b. Wound is contracting and epithelializing. Important to note is that even ischemic, infected wounds in the elderly (this patient also had venous reflux and took systemic steroids) are expected to heal as long as comprehensive treatment is initiated immediately.

stasis ulcers, and extremity amputations in patients with diabetes. All chronic wounds in elderly patients must be treated with the expectation that the wound will heal to 100% closure, except in patients with ischemia and osteomyelitis. To achieve this, all elderly patients who are bed-bound or have any wound, should be examined every day, and any new wound in these patients should be treated immediately.

Our findings demonstrated that elderly patients can and should be expected to heal despite experimental and clinical evidence of impairment in physiological processes. Clearly, these processes can be reversed by standard treatment, as well as by use of growth factors and cell therapy when needed. Although age is implicated as one of the factors that affect wound healing, wounds in the aged heal despite associated morbidities —such as decreased organ function, spinal cord injury, concomitant disease, nutritional deficiencies, diabetes, uremia, and other factors—as is evident by the findings presented herein. Early treatment is especially important for the elderly population, because these patients, more than any other age group, have difficulty compensating with morbidities and complications associated with chronic wounds. This report does not advocate any one specific therapy; rather, emphasis is placed on the initiation of a comprehensive treatment plan that follows a standard protocol specific to each type of wound.

Future directives must delineate the physiological impairments associated with each specific type of chronic wound (i.e., diabetic foot ulcers) within the elderly population. One should not assume that the elderly have impaired angiogenesis and, therefore, impaired healing. Rather, it is vital to differentiate mechanisms underlying decreased angiogenesis in an elderly patient with, for example, a heel ulcer from those underlying decreased angiogenesis in an elderly patient with, for example, a sacral pressure ulcer. This differentiation will define which existing therapies and technologies can be applied to elderly patients with specific types of chronic wounds, and guide the development of new therapies for specific types of wounds and in specific locations in the elderly population. By targeting a specific population, a treatment plan will encompass the age of the patient as well as type, location, and pathogenesis of the wound and, subsequently, increase the number of patients who will have 100% healing as well as accelerate the time to closure.

When an elderly patient is first seen with a chronic wound, it is critical to immediately develop a plan of treatment that involves the geriatrician and wound-care clinician, as well as determine the proper topical treatment. If this procedure is followed, we expect most patients with chronic wounds, regardless of age, to heal (except in the presence of ischemia and osteomyelitis). In the future, as new therapies develop, these wounds should heal more rapidly, which is of particular importance in the elderly, because this population suffers the most from the complications associated with chronic wounds.

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