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# Chronic Wound Repair and Healing in Older Adults: Current Status and Future Research

**Lisa Gould, MD, PhD**[1], **Peter Abadir, MD**[2], **Harold Brem, MD**[3,4], **Marissa Carter, PhD**[5], **Teresa Conner-Kerr, PhD**[6], **Jeff Davidson, PhD**[7], **Luisa DiPietro, DDS, PhD**[8], **Vincent Falanga, MD**[9], **Caroline Fife, MD**[10,11], **Sue Gardner, PhD, RN**[12], **Elizabeth Grice, PhD**[13], **John Harmon, MD**[14], **William R. Hazzard, MD**[15], **Kevin P. High, MD**[16,17], **Pamela Houghton, PhD**[18], **Nasreen Jacobson, PhD**[19], **Robert S. Kirsner, MD, PhD**[20], **Elizabeth J. Kovacs, PhD**[21], **David Margolis, MD, PhD**[22], **Frances McFarland Horne, PhD**[23], **May J. Reed, MD**[24], **Dennis H. Sullivan, MD**[25], **Stephen Thom, MD, PhD**[26], **Marjana Tomic-Canic, PhD**[27], **Jeremy Walston, MD**[2,28], **Jo Anne Whitney, PhD**[29], **John Williams, PhD**[30], **Susan Zieman, MD**[30], and **Kenneth Schmader, MD**[31]

[1]Wound Recovery and Hyperbaric Medicine Center, Kent Hospital, Warwick, Rhode Island [2]Division of Geriatrics and Gerontology Medicine, Johns Hopkins University, Baltimore, Maryland [3]Department of Wound Healing and Regenerative Medicine, Winthrop University Hospital [4]School of Medicine, Stony Brook University, Mineola, New York [5]Strategic Solutions, Inc., Cody, Wyoming [6]Department of Physical Therapy, Winston-Salem State University, Winston-Salem, North Carolina [7]Department of Pathology, Microbiology, and Immunology, School of Medicine, Vanderbilt University, Nashville, Tennessee [8]Center for Wound Healing and Tissue Regeneration, University of Illinois at Chicago, Chicago, Illinois [9]Department of Dermatology, School of Medicine, Boston University, Boston, Massachusetts [10]Department of Geriatrics, Baylor College of Medicine, Houston [11]St. Luke\s Wound Center, The Woodlands, Texas [12]College of Nursing, University of Iowa, Iowa City, Iowa [13]Penn Institute for Immunology, University of

Address correspondence to Lisa Gould, Wound Recovery and Hyperbaric Medicine Center, Kent Memorial Hospital, 455 Tollgate Road, Warwick, RI 02886. lgould44@hotmail.com.

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Pennsylvania, Philadelphia, Pennsylvania [14]Department of Surgery, Johns Hopkins University, Baltimore, Maryland [15]Gerontology and Geriatric Medicine, School of Medicine, Wake Forest University, Winston-Salem, North Carolina [16]Department of Internal Medicine, School of Medicine, Wake Forest University, Winston-Salem, North Carolina [17]Section on Infectious Diseases, School of Medicine, Wake Forest University, Winston-Salem, North Carolina [18]School of Physical Therapy, Western University, London, Ontario, Canada [19]Smith & Nephew, Fort Worth, Texas [20]Department of Dermatology and Cutaneous Surgery, Miller School of Medicine, University of Miami, Miami, Florida [21]Department of Surgery, Burn and Shock Trauma Research Institute, Loyola University, Chicago, Illinois [22]Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania [23]Association of Specialty Professors, Alexandria, Virginia [24]Division of Gerontology and Geriatric Medicine, University of Washington, Seattle, Washington [25]Department of Geriatrics, University of Arkansas for the Medical Sciences, Little Rock, Arkansas [26]Department of Emergency Medicine, University of Maryland, Baltimore, Maryland [27]Wound Healing and Regenerative Medicine Research Program, Miller School of Medicine, University of Miami, Miami, Florida [28]Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland [29]School of Nursing, University of Washington, Seattle, Washington [30]National Institute on Aging, Bethesda, Maryland [31]Geriatric Research, Education and Clinical Center, Durham Veterans Affairs Medical Center and Duke University Medical Center, Durham, North Carolina

## Abstract

Older adults are more likely to have chronic wounds than younger people, and the effect of chronic wounds on quality of life is particularly profound in this population. Wound healing slows with age, but the basic biology underlying chronic wounds and the influence of age-associated changes on wound healing are poorly understood. Most studies have used in vitro approaches and various animal models, but observed changes translate poorly to human healing conditions. The effect of age and accompanying multimorbidity on the effectiveness of existing and emerging treatment approaches for chronic wounds is also unknown, and older adults tend to be excluded from randomized clinical trials. Poorly defined outcomes and variables; lack of standardization in data collection; and variations in the definition, measurement, and treatment of wounds also hamper clinical studies. The Association of Specialty Professors, in conjunction with the National Institute on Aging and the Wound Healing Society, held a workshop, summarized in this article, to explore the current state of knowledge and research challenges, engage investigators across disciplines, and identify research questions to guide future study of age-associated changes in chronic wound healing.

### Keywords

chronic wound; pressure ulcer; diabetic foot ulcer; venous leg ulcer; wound repair; wound healing

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Chronic wounds, which include venous leg ulcers (VLUs), diabetic foot ulcers (DFUs), arterial insufficiency, and pressure ulcers (PUs), disproportionately affect older adults and impose substantial morbidity and mortality on millions of older Americans. The great

majority of chronic wounds are associated with conditions more common in older than younger individuals, including vascular disease, venous insufficiency, unrelieved pressure, and diabetes mellitus. In addition, an increasing number of older adults are undergoing surgery and are at risk of wound complications. Fundamental questions remain about the effect of aging on wound healing and the mechanisms of wound repair and tissue regeneration in older adults. Furthermore, few well-designed clinical trials have explored the treatment of wounds in older adults, leaving clinicians with scant evidence to guide optimal wound management, but with better scientific and clinical tools, along with an increasing number of highly motivated and talented investigators, a critical juncture to address these issues is being reached.

This workshop convened a transdisciplinary group of experts in the fields of wound repair and regeneration, skin aging, geriatric conditions, and gerontology from across the United States and Canada and program staff and scientists from the National Institute on Aging; the National Institute of Diabetes and Digestive and Kidney Diseases; the National Heart, Lung, and Blood Institute; and the National Institute of Nursing Research. The workshop aimed primarily to review current knowledge in epidemiological, basic science, and clinical topics; identify gaps in that knowledge; and develop a research agenda. Participants summarized research priorities and generated questions for future research (Table 1).

## EPIDEMIOLOGY OF CHRONIC WOUNDS IN OLDER ADULTS

The burden, particularly prevalence and incidence, of chronic wounds is unclear because of underreporting, poor definition of “chronic wound,” and inaccurate diagnostic coding for wound care. Many epidemiological studies do not distinguish between prevalence and incidence, and they often focus on endpoints, such as lower-extremity amputations (LEAs), which are easier to define and measure. Thus, estimates of prevalence and incidence vary between studies. Despite these limitations, studies indicate that the incidence of chronic wounds increases with age even into late life.[1,2] Studies using the General Practice Research Database in the United Kingdom have found that VLU incidence is three to four times as high and PU incidence five to seven times as high in persons aged 80 and older than in those aged 65 to 70.[1,2] Care for chronic wounds costs approximately $10 billion annually in the United States,[3] and it is likely that wound care in adults aged 65 and older accounts for the majority of these costs.

Chronic wounds have a profound effect on quality of life (QOL), as assessed using generic and wound-specific instruments or according to health utility.[4–6] The effect is similar to that of kidney or heart failure, and QOL decline is particularly precipitous in older adults, although overall QOL in older populations with chronic wounds is poorly understood. Existing measures do not differentiate age-related differences in the effect of chronic wounds between community-dwelling older adults and those in long-term care. Data from the U.S. Wound Registry indicate that individuals in outpatient wound centers have an average of eight comorbid conditions,[7] but there is no clear distinction between the effect on QOL of chronic wounds and that of comorbidities.[8,9] Furthermore, QOL as a function of wound severity, etiology, and complications is poorly understood.

Although people of all races and ethnicities experience chronic wounds, there are racial and ethnic disparities in wound severity at presentation and in subsequent treatment of wounds, although these disparities are more likely to reflect socioeconomic differences and clinician bias than true differences in the wounds based on race or ethnicity. PU incidence in African-American nursing home residents is more than 1.5 times that of white residents.[10–13] It is likely that that disparity arises from differences in diagnosis and care; PU incidence is greater in white residents who live in nursing homes where the majority of residents are African American than in those who live in nursing homes where the majority of residents are white.[10–13] LEA risk is also higher in African Americans and Native Americans, than in non-Hispanic whites, and it varies according to culture in Hispanic individuals,[14–16] although the incidence of diabetes mellitus is also higher in non-white individuals, and race and ethnicity is less of a predictor of LEA than other factors, such as differences in rates of peripheral vascular disease and smoking. Time to amputation is shorter for African Americans than for whites, but this disparity also might arise from differences in prevention and care; African Americans tend to receive less preventive care, and whites are more likely to receive revascularizations.[17–19]

## BASIC SCIENCE OF WOUND REPAIR AND HEALING

### Biology of Wound Healing, Chronic Wounds, and Aging

The complex process of wound healing occurs in overlapping phases: inflammation, proliferation, angiogenesis, epidermal restoration, and wound contraction and remodeling.[20] Important cell types in this process are platelets, which recruit inflammatory cells and form a provisional matrix, and macrophages, which include several phenotypes and regulate the cytokine environment in the wound, which influences proliferative responses and wound closure.[21] Matrix metalloproteinases (MMPs) are active throughout wound healing, aiding in phagocytosis, angiogenesis, cell migration during epidermal restoration, and tissue remodeling.

In chronic wounds, resident cells proliferate less and have a morphology similar to that seen in senescent cells. Fibroblasts from chronic VLUs, particularly ulcers of long duration, have poorer responses to platelet-derived growth factor (PDGF),[22] alterations in transforming growth factor beta (TFG-$\beta$) and TGF-$\beta$ type II receptor expression,[23] and abnormal phosphorylation of critical signal transduction proteins.[24] The low receptor expression in cells in these wounds is similar to that in cells exposed to low oxygen tension, suggesting that chronic wounds are hypoxic.[24]

Aging also is associated with alterations in wound healing. In a diabetic mouse model, the healing of burns is delayed in older mice as a result of diminished hypoxia-inducible factor 1 expression, fewer bone marrow–derived angiogenic cells (BMDACs), and dampened response and homing in BMDACs that are present (Figure 1).[25,26] Aging also is associated with delays in macrophage and T-cell infiltration, angiogenesis, and epithelialization.

The properties of the extracellular matrix (ECM) and its contribution to wound-healing changes throughout the life span (Table 2).[27] Whereas younger skin can mount a robust response by producing ECM that can adapt to the mechanical demands of an injury, older

skin has atrophied and has a prolonged, blunted healing response[28] with inflammation and differences in signal transduction that result in inferior in ECM production. Healing in older animals also involves a protective and noninflammatory response characterized by lack of matrix molecule production and less scarring. Work in an in vitro model of aged rat skin suggests that age-associated disadvantages in healing may arise from overexpression of MMPs, particularly MMP2,[29] consistent with findings that protease expression and activity are greater in older humans.[30] Age-related changes in hormonal status affect repair. MMPs, particularly MMP2, are high principally in older postmenopausal women, and estrogen replacement therapy can stimulate the migration and proliferation of keratinocytes and elaboration of matrix.[30]

The microcirculation (arterioles, capillaries, venules) plays a critical role in wound healing. The vasoregulation of the microcirculation of aged skin is impaired, which reflects changes in inflammatory responses, fewer progenitor cells, and declines in circulatory mediators.[31] Age-associated delays in microvascular responses to stressors lead to impaired temperature regulation and greater likelihood of tissue hypoperfusion,[31] which inhibits wounds from reaching the angiogenic stage of repair. Optimal healing strategies after surgery and other stressors must therefore use multifactorial approaches to address changes in the microcirculation in older adults. Potential strategies include better use of existing vessels to optimize vasodilation (e.g., physical activity, pneumatic compression, pharmacological mediators);[32–34] optimization of inflammatory and other cellular responses (e.g., stem cells);[35,36] and strategies to address deficiencies in growth factors, sex steroids, and the extracellular matrix.[37,38]

## MOLECULAR AND CELLULAR PROCESSES IN WOUND HEALING

### Inflammation

Under normal wound healing conditions, early macrophages promote inflammation, and later macrophages clear neutrophils and switch to a reparative phenotype, but in the wounds of diabetic mice, macrophages fail to clear dying neutrophils and therefore remain in a proinflammatory phenotype.[39] Similarly, in humans and mice, VLUs contain high levels of iron; thus, macrophages take up more iron and remain in a proinflammatory state.[40] Although impairment in the switch from the proinflammatory to reparative phenotype is involved in chronic wounds, the intermediate steps between the two phenotypes are not clear. Whether an alteration in the macrophage switch affects wound healing in aging is unknown.

Excisional wounds heal more slowly in older mice than in young adult mice[41] as a result of greater macrophage infiltration, especially at earlier phases of wound repair. Age-associated aberrations in macrophage functions decrease or delay vascularization, collagen deposition, and collagen remodeling.[42] In contrast, scald wounds heal more slowly in older than younger mice, as a result of lower chemokine levels.[43] Neutrophil depletion, which enhances wound healing in younger mammals,[44] delays wound closure in aged mice.[45] All these changes may arise from age-associated increases in basal or constitutive inflammation, which occur even in healthy individuals. Age-associated inflammation and delays in wound healing may have particular consequences for infection. In a mouse model of wounds

inoculated with *Staphylococcus aureus*, older mice fail to clear the infection (Figure 2) and show less neutrophil chemotaxis, greater bacterial colonization, and slow macrophage infiltration.[46]

Age-associated inflammation is characterized by sustained high levels of proinflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor alpha, and by declines in growth factors that are important for wound healing. TGF-β, which remains high during chronic inflammation, may promote the transformation of acute wounds into chronic ones by contributing to fibrotic replacement and scarring and by inhibiting reepithelialization.[47] Angiotensin receptor signaling influences TGF-β expression. With diabetes mellitus or age, skin has greater expression of angiotensin II and the proinflammatory, vasoconstrictive AT1 receptor-signaling pathway.[48–50] Treatment with the angiotensin receptor blocker (ARB) losartan improves muscle remodeling after injury,[51] and individuals with diabetes mellitus taking ARBs are less likely to undergo amputation than those taking angiotensin-converting enzyme inhibitors,[52] indicating that angiotensin receptor signaling increases fibrosis and satellite cell deactivation and may serve as a target for wound healing.

## MITOCHONDRIAL DYSFUNCTION AND OXIDATIVE STRESS

Mitochondria provide energy and produce reactive oxygen species to drive the increased mitotic and synthetic activity necessary for wound healing. Oxidative stress is also necessary for cellular signaling, the clearing of bacteria, the transition into the proliferative phase of wound healing, and enhancement of angiogenesis through the production of mediators such as nitric oxide and the hypoxia-inducible factor 1α pathway.[53] Because of high energy needs during wound repair and to avoid the overuse of mitochondria as the sole energy source, the process of adenosine triphosphate generation shifts from oxidative phosphorylation to glycolysis. Although glycolysis is less efficient than oxidative phosphorylation, it probably protects the mitochondrial pool from increasing damage related to oxidative stress.[54] Furthermore, efficient mitochondrial turnover mechanisms in the form of mitophagy and mitobiogenesis are required to maintain a healthy pool of mitochondria, yet the skin is exposed to higher levels of extrinsic insults than other organs, which probably lead to dysfunctional mitochondria, low adenosine triphosphate production, and oxidative damage that triggers mitochondrial turnover. Skin mitochondria, particularly in exposed skin, have a greater incidence of mitochondrial deoxyribonucleic acid mutations with older age,[55] indicating not only an increase in the number of dysfunctional mitochondria but also defects in eliminating them. The chronic inflammation seen with age and chronic conditions increases the number of dysfunctional mitochondria, and older age has been associated with lower levels of antioxidants,[56] although the link between age-associated mitochondrial dysfunction and impaired wound healing has been poorly studied.

## MICROBIAL BURDEN

The effect of microbial burden on wound healing is unknown and probably underestimated. Traditionally, studies of microbial burden have relied on culture-based techniques and therefore have excluded the vast majority of microbes. Because culture-based studies also exclude bacteria that rely on microbial community interactions, they provide little

information about the biofilm, a factor thought to be critical in wound healing. Recent studies using 16S ribosomal ribonucleic acid–based gene sequencing and quantitative polymerase chain reaction have revealed that the skin and wounds have rich microbiomes with marked variability according to body region, wound type, and sampling method.[57–59] In particular, *Staphylococcus*, *Anaerococcus*, *Corynebacterium*, and anaerobic species appear to contribute to microbial burden and wound behavior; for example, a genomic study of DFUs suggested a negative correlation between *Staphylococcus* burden and the depth and duration of the ulcer.[57] Bacterial community structure also has been correlated with clinical data. Of 30 individuals with open fractures related to traumatic injury, bacterial community structure differed between those who later developed complications and those who did not, as well as between upper and lower extremity wounds.[60] Further study using genomic sequencing techniques and clinical correlations might identify microbial burden associated with the development of chronic wounds, but the best collection methods are still unknown, and more standardization is needed to facilitate comparisons of studies. Moreover, rodent studies suggest that aging affects bacterial clearance, but no microbiome research has focused on older adults.

## BASIC SCIENCE RESEARCH CONSIDERATIONS

In vitro models have yielded much information on the basic biology of wound healing, and more-complex, -reproducible, and -relevant systems, such time-lapse photography to measure wound parameters, are available, but the mechanical environment in which these models are studied differs from the human environment. Attempting to study too many variables in these models can hinder new understanding, yet models that mimic the combination of comorbid conditions that occur in aged humans are needed. Stem cell research is promising, but concerns about immunogenicity, teratomas and other malignancies, the ability to maintain pluripotency, and limited supply hamper use of stem cells, as do ethical concerns.

Many studies in wound repair have relied on animal models, particularly mouse models, to increase understanding of the phases of wound healing and the changes that occur with age, but skin morphology and the mechanisms of wound repair differ markedly between mice and humans. Pig skin is closest to human skin,[61] but a long life span and higher maintenance costs limit the utility of pig models. Moreover, studies in animal models have focused primarily on excisional wounds; incisional wounds, abrasions, and burns are poorly studied. Furthermore, there are no models that mimic chronic wounds or the comorbidities commonly seen with human aging.

It has been difficult to identify predictive, diagnostic, and indicative biomarkers of wound healing because of the multifactorial pathogenesis and the heterogeneity of sampling spanning between and within wound types. Little is known regarding the contribution of aging in the context of specific biomarkers in older adults. Gene expression profiles have been identified in biopsies from VLUs, DFUs, and other chronic wounds, yielding a large number of potential biomarkers of nonhealing wounds,[62–65] but the correlations between these tissue-based markers and wound healing outcomes and how to harness this information into predictive and diagnostic tools are not clear. Rapid tests that detect high

MMP levels in wounds can identify a subset of individuals with poor wound healing,[66–70] but variability in obtaining and measuring specimens limit these tests. It is still not clear which individuals might heal with standard of care, whether observed differences represent cause or effect, or how age influences such tests. Furthermore, polymerase chain reaction–based identification of bacterial species is under development as an approach to point-of-care diagnostics related to polymicrobial and biofilm-infected wounds.[71,72] Substantial research is needed to identify, evaluate, and validate biomarkers related to wound healing in general and specifically in older adults.

## CLINICAL RESEARCH ON CHRONIC WOUNDS

### Novel Therapeutic Approaches

**Cellular and Tissue-Engineered Products—**Cellular and tissue-engineered products are often combined with standard-of-care approaches such as moist wound healing, compression, and offloading. A new product that distinguishes itself from current cellular and tissue-engineered products is a topical wound spray (HP802–247), which delivers a specific, optimized ratio of primed allogeneic fibroblasts and keratinocytes directly to the ulcer in a fibrin spray.[73,74] Phase 2b study data indicate that HP802–247 promotes significant healing of VLUs, with the odds of wound healing being 2.75 times as great with HP802–247 than with the vehicle control.[73,75] Confirmatory Phase 3 clinical trials are under way in the United States and Europe. In general, a lack of well-controlled and comparative data, clear mechanism(s) of action, and clear definitions that distinguish between cellular therapies, advanced therapies, and dressings has limited development of evidence-based clinical protocols for the therapeutic use of cellular and tissue-engineered approaches. The need for better defined regulatory and reimbursement pathways has also hampered such development. The potential influences of age on cellular and tissue-engineered products are also poorly characterized.

**Negative-Pressure Wound Therapy—**Although data from randomized controlled trials and meta-analyses suggest that negative-pressure wound therapy is effective in older adults,[76–82] few studies have focused specifically on older adults, and there are not enough data for a clear recommendation. Many variables that may influence wound healing are defined inadequately in these studies,[83] and the mechanism of action for negative-pressure wound therapy is poorly understood. Primary effects may include macrodeformation (wound contraction) and microdeformation (the microscopic interaction between the wound and dressing). Potential secondary effects include high cell proliferation and granulation tissue, perhaps as a result of changes in bacterial levels or cell stress.[84–90]

**Hyperbaric Oxygen Therapy—**The benefit of hyperbaric oxygen therapy is even less clear. In a recent meta-analysis of six randomized controlled trials and six observational studies, the observational studies showed a benefit, but the randomized trials did not,[91] and none of the studies focused on older adults. A retrospective study also failed to show efficacy or effectiveness.[92] Some animal data suggest that hyperbaric oxygen therapy is effective at all ages.[93,94] New mechanistic studies of hyperbaric oxygen therapy are focusing on stem cells. Vasculogenic and mesenchymal stem cells incur damage with

chronological and replicative aging, resulting in poorer differentiation than in younger cells[95–97] and lack of mobilization,[98–100] but few clinical data have correlated circulating cells with wound healing.[101]

**Electrical Stimulation—**Physical therapy approaches also show promise for wound healing. Although electrotherapy has not been assessed in large clinical trials, a meta-analysis of several small trials with individuals of all ages has found that it effectively promotes wound closure.[102] Electrotherapy improves blood flow and prevents PUs in individuals with spinal cord injury,[103] and it may improve take of grafts and flaps, improve vascularization, reduce necrosis, and increase angiogenesis in patients with VLUs or critical limb ischemia.[104–106]

**Ultrasound—**Low-frequency (22.5–35 kHz) ultrasound applied in contact rapidly debrides the wound surface and is a fairly comfortable procedure;[107] many individuals decline pretreatment with lidocaine after one or two treatments. Several studies have shown that low-frequency contact ultrasound works synergistically with antibiotics to provide a better kill rate of antibiotic-resistant strains of bacteria and biofilms than antibiotics alone.[108–111] Low-frequency ultrasound also reduces antimicrobial resistance in vitro.[111] Data from a small clinical study of 17 individuals aged 32 to 83 with ulcers of mixed etiologies suggest that low-frequency ultrasound promotes healing of all wounds without antibiotics.[109] The effectiveness of low-frequency ultrasound in healing chronic wounds of older adults is unclear. Larger randomized clinical trials are under way in Canada (NCT01973361) and Australia,[112] but additional large, multicenter trials are needed.

## Nutrition

Older adults categorized as undernourished are at risk of developing PUs and other complex wounds,[113,114] although factors other than inadequate nutrient intake may confound this association.[115] Commonly used putative markers of nutritional deficiency have low sensitivity and specificity as nutritional indicators in these older high-risk populations.[115] Most of these individuals have multiple additional comorbidities, such as ongoing inflammation, disuse atrophy, or other metabolic disturbances, and these comorbidities can have a greater effect than nutritional intake in altering the putative nutritional markers.[116] In addition, despite a wealth of nutritional studies, no consensus has been reached on optimal nutritional care for older adults with chronic wounds. The recommended daily protein allowance assumes that adults are healthy, consume high-quality protein, and have adequate energy intake.[117] Recognizing that inflammation, the adequacy of energy intake, and other stressors common in older adults with complex wounds influence protein requirements, the Agency for Healthcare Research and Quality developed recommendations for protein intake for individuals with uncomplicated PUs, but these estimates are based on anecdotal evidence.[117,118] There is conflicting evidence that dietary interventions or commercial supplementation are effective in preventing PUs or accelerating healing.[118–121] Of the few studies that report evidence of benefit, most are methodologically weak, and their findings have yet to be verified.[119,121–124] Further research is needed in this area, but disentangling nutritional needs from other factors affecting metabolic response to injury, especially when multiple comorbid conditions are present, remains a challenge.[114,120,125]

### Clinical Research Considerations

The majority of wound care is performed in the outpatient setting, and clinical trials therefore focus on outpatient care, but the presence of a wound significantly affects inpatient costs, length of hospital stay, and discharge planning. Thus, future clinical studies will require a clear definition of hospital-based wound healing in older adults. Variations in data collection and in the definition, measurement, and treatment of wounds in older adults have hindered the development of such a definition. Measurable outcomes also must be defined, and several have been suggested. A well-structured electronic medical record that follows the individuals through the continuum of care facilitates the measurement of these variables for clinical outcomes and research (Table 3).

Approval of products or devices by the U.S. Food and Drug Administration (FDA) is a major driver in the design and conduct of clinical trials,[126] but the approval process in general is long and expensive, and only one in 25 products is eventually approved. Approval is even more constrained for wound care. The FDA has approved only three products for wound care in the past 20 years[127] and has defined only one endpoint—complete healing—for wounds. Thus, traditional, FDA-driven, randomized trials, albeit effective for assessing efficacy, may not inform clinical decision-making for wound care.[126] Other study designs, such as pragmatic or comparative effectiveness approaches, might be more appropriate.[128]

A critical concern regarding clinical trial design for older adults is that of inclusion criteria. Clinical trial populations tend to be homogenous, and many comorbidities associated with older age are excluded. Age itself can be an exclusion criterion, but it is not clear that it should be. A meta-analysis of 10 trials has found that it is wound chronicity, rather than age, that plays a strong role in healing in individuals receiving standard care for DFUs.[129] Another study found that the area and duration of the wound, but not age, influence healing of VLUs after spray therapy.[130] Thus, age does not appear to be a significant factor in the response to wound treatment, although it can be an important predictor, as the formula derived from a clinical database for an ulcerated leg severity assessment illustrates.[131]

## UNANSWERED QUESTIONS, FUTURE DIRECTIONS, AND RESEARCH CHALLENGES

Future research will require common definitions and standardized procedures for data collection and will need to address the analytical challenges associated with studying older adults, such as population heterogeneity, missing data from death or dropout, limited sample sizes, and variable follow-up times. Valid clinical and individual measures, particularly those of most value to the individuals, also are needed. With better measures and more data, the FDA might accept additional endpoints for clinical trials in wound care, particularly in older adults. Common comorbidities are a major concern in geriatrics and therefore should be explored in clinical trials and in basic and preclinical studies. Issues related to polypharmacy also should be explored. Specific research questions regarding wound healing in older adults are listed in Table 1.

Because the concept of chronic wounds crosses many disciplines, more collaboration is needed to answer common questions. Transdisciplinary collaboration between clinicians and

basic scientists can facilitate development of animal models that more closely mimic human wound closure. Interaction between wound care clinicians and basic scientists can identify optimal strategies to obtain and use clinical samples, and multicenter collaborations among wound care clinicians, geriatricians, and gerontologists will improve clinical trial design for older adults and incorporate measures of QoL. Investigators studying wound healing can also learn from other fields, such as oncology, and engagement with government, industry, data-mining companies, and consulting groups might provide access to public and proprietary databases and information focused on public health. Potential resources are listed in Table 4.

Future research on wound healing in older adults will also benefit from efforts to address structural challenges in the research enterprise. Well-conducted education and implementation science studies can improve the ability of front-line providers to provide critical wound care, aid in convincing hospital and nursing home administrators of the value of educational programs, and increase implementation of preventive approaches. Perverse incentives related to the fee-for-service model, which has traditionally ignored prevention, also must be addressed. Moreover, development of a formal wound care specialty would promote consensus on standard wound care, provide a more-unified approach to wound research, and perhaps improve and expand cross-disciplinary educational approaches.

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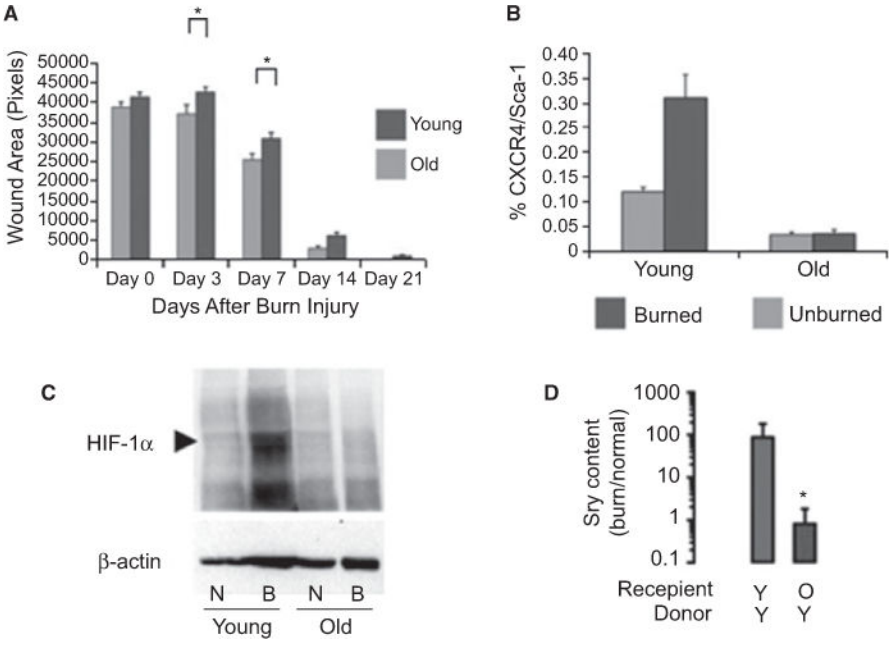


**Figure 1.**

Burn wound repair is delayed in aged mice. (A) Wound area was evaluated 0, 3, 7, 14, and 21 days after burn injury in 2-month-old (young) versus 2-year-old C57BL/6J mice. **P* < .05 versus young mice. (B) Bone marrow–derived angiogenic cells were identified using fluorescence-activated cell sorting as CXCR4+/Sca-1+. (C) Human inducibility factor (HIF)-1a concentrations in response to burn injury are lower in aged than younger mice. (D) Bone marrow–derived angiogenic cells from young male mice (Y) administered through tail vein injection to recipient female mice with burn wounds were less able to home in older recipients (O) than in younger ones (Y). Donor cells were identified using the *Sry* gene as a marker. **P* < .01 versus young recipients. N = normal; B = burned. Adapted from Zhang X et al.[25]

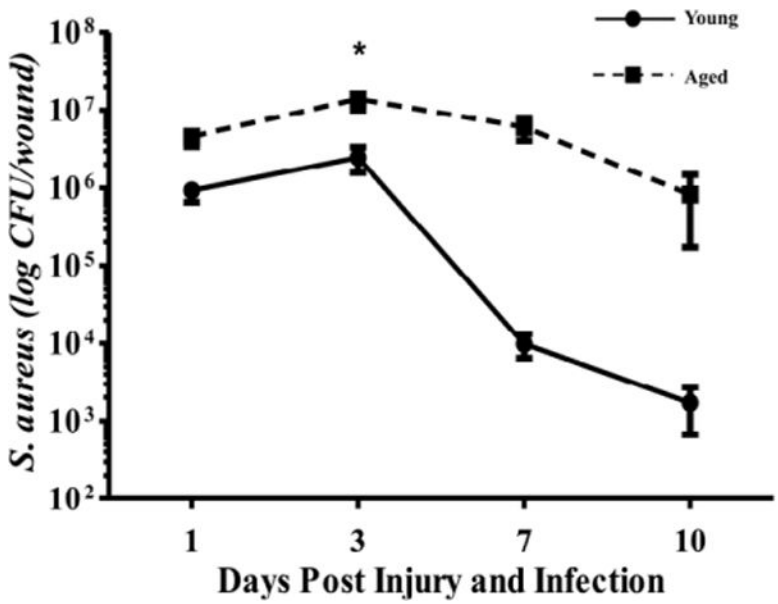


**Figure 2.**

Implications of age-associated inflammation for infection. In a mouse model, older mice inoculated with *Staphylococcus aureus* fail to clear infection, unlike younger mice. *$P < .001$ versus young at same time point using two-way analysis of variance. Source: Brubaker et al.[46]

## Table 1

Research Questions for Wound Healing in Older Adults

| Category | Research Questions |
|---|---|
| Epidemiology and quality of life | What is the burden of illness due to chronic wounds in populations of older adults? |
| | What is the frequency of multiple wounds and recurrent wounds in older adults? |
| | What is the reason for racial and ethnic disparities in prevention and management of chronic wounds in older adults? |
| | What is the effect of wound-associated pain on quality of life and function? |
| | What are the effects of other comorbidities in conjunction with chronic wounds, with respect to quality of life? |
| | What are the effects of socioeconomic status, living status, and other social factors on chronic wounds and quality of life? |
| | How does adhering to evidence-based clinical guidelines affect complications and quality of life? |
| | Does healing a chronic wound necessarily improve quality of health? |
| | What is the effect of treatment regimens or evidence-based guidelines for chronic wounds on quality of life? |
| Basic biology of wound healing, chronic wounds, and aging | What causes acute injuries to become chronic wounds? |
| | How can immune cells in the wound environment, or recruitment of immune cells to the wound, be modulated to harness benefit? |
| | What strategies can be used to reverse macrophage impairment? |
| | What factors regulate or activate macrophage phenotypes in wound repair? |
| | What are the mechanisms underlying endothelial and epidermal stem cell activation and homing to the wound site? |
| | What are the roles of proliferation and apoptosis in acute versus chronic wounds? |
| | What are reasons for delayed chemotaxis and lack of neutrophil function in chronic wounds? |
| | How does neutrophil depletion delay wound closure with advanced age? |
| | What are the mechanisms for matrix metalloproteinase overproduction with aging in chronic wounds? |
| | What drives the changing composition and properties of extracellular matrix during development and aging? |
| | What are the contributions of aging and comorbidities to the development of chronic wounds? |
| Molecular and cellular processes | |
| Inflammation | What mechanisms contribute to low human inducibility factor 1a expression? |
| | Does aging alter transforming growth factor beta signaling in chronic wounds? |
| | How important are changes in inflammatory responses to age-related changes in wound healing? |
| | How does inflammation affect the wound healing process in older adults? |
| | What is the optimal inflammatory response that will support rapid repair yet effectively reduce infection? |
| | Can manipulating inflammation alone force chronic wounds to heal? |
| Oxidative stress | What is the role of specific mitochondrial deoxyribonucleic acid damage in impaired skin healing? |
| Microbial burden | Which microbiota are beneficial, and which are problematic for wound healing? |
| | How does microbial bioburden in the wound influence systemic and local immune responses? |
| | How does age influence microbial burden in wounds and subsequent wound healing? |
| Clinical care | |

| Category | Research Questions |
|---|---|
| General | What is the clinical significance of delayed wound healing in older adults? |
| | What is the significance of delayed wound healing from the individual's point of view? |
| | Should wound care guidelines differ for older adults, accounting for heterogeneity and quality of life? |
| Novel therapeutic approaches | What interventions effectively improve microcirculation and wound healing with aging? |
| | What is the effect of wound therapies on universal outcomes, such as functional status, pain, physical impairment, mobility, and cognitive impairment, as opposed to wound-specific outcomes? |
| | What is the effect of multicomponent interventions on individual- and wound-specific outcomes? |
| | Are there special considerations related to older adults with chronic wounds and dementia? |
| | During surgery, what steps can anesthesiologists take to mitigate risk for chronic or nonhealing wounds? |
| | How do various wound treatments affect microbial burden? |
| | What new therapeutics can be developed based on the microbiome? |
| | How should cellular therapy be positioned in wound care? |
| | What potency assays are available to regulate cellular therapies? |
| | What is the effectiveness of physical modalities such as electrical stimulation and ultrasound in older adults? |
| | What is the effect of exercise on wound healing? |
| | What interventions effectively prevent chronic wounds in older adults? |
| Nutrition | Can individuals be better categorized on the spectrum from cachexia to starvation, and can this categorization aid in determining the most-effective nutritional treatment strategies? |
| | What is the optimal protein and energy intake for older adults with chronic wounds, especially at weight extremes? |
| | Is there a role for complete and various modular nutritional supplements, vitamin and mineral supplementation above the U.S. recommended daily intake, or appetite stimulants and anabolic steroids in the care of individuals with chronic wounds? |
| | Are complete or modular commercial nutritional supplements better than regular foods? |

## Table 2

Properties in Cutaneous Extracellular Matrix (ECM) and Wound Healing over the Life Span[27]

| Age | Properties |
|---|---|
| Fetal | Highly regenerative skin |
| | Large amount of cell mobility in a fragile ECM |
| | ECM rich in collagen III and hyaluronic acid |
| | Little inflammation in response to injury |
| | Scarless healing |
| Juvenile | Massive production of type I collagen |
| | Moderate and transient inflammation |
| | Cellular response in compliant ECM |
| Early adult | Scarring properties at maximum |
| | High production of type I collagen |
| | Fibrotic response in stiff ECM |
| Aged adult | Prolonged inflammation |
| | High matrix metalloproteinase and elastase expression |
| | Low expression of transforming growth factor beta |
| | Weakened cellular response in an atrophic ECM |

**Table 3**

Potential Outcomes for Clinical Studies of Wound Healing in Older Adults

| |
|---|
| Synergy between age and comorbidities[132] |
| Pathology of tissue left behind in the wound[133] |
| Costs of nonhealing wounds[134] |
| Goals for healing at the time of wound presentation[135,136] |
| Effects of standardized clinical decision support based on electronic medical records[137] |
| Quality of life |
| Functional status |
| Morbidity |
| Pain |
| Level of independence |
| Sepsis |
| Prevention of amputation and mortality |
| Palliative care versus healing |

**Table 4**

Available or Forthcoming Resources

| Resource | Purpose |
|---|---|
| Infrastructure, databases, and registries | |
| U.S. Wound Registry (www.uswoundregistry.com) | Registry of de-identified data encompassing 100 hospital-based outpatient wound centers in 32 states and Puerto Rico |
| | Designated by the Centers for Medicare and Medicaid Services as a Qualified Clinical Data Registry for the Physician Quality Reporting System |
| Stony Brook University Clinical Decision Support system | Institutional review board–approved, electronic medical record–based system to facilitate enrollment in clinical studies |
| Measures | |
| EQ-5D | General quality-of-life instruments |
| Medical Outcomes Study 36-item Short-Form Health Survey | |
| Sickness Impact Profile | |
| Cardiff Wound Impact Schedule | Wound-specific quality-of-life instruments |
| Freiburg Life Quality Assessment | |
| Funding sources | |
| R21/R33 mechanism, National Institute on Aging | Link institutions to create infrastructure with multiple areas of expertise |
| | Infrastructure to support clinical trials evaluating questions for which the sum is greater than all the parts |