PERSPECTIVE ARTICLE

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

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 Surgery, Johns Hopkins University, Baltimore, Maryland,
4. National Institute on Aging, Bethesda, Maryland,
5. Department of Emergency Medicine, University of Maryland, Baltimore, Maryland,
6. Department of Wound Healing and Regenerative Medicine, Winthrop University Hospital and School of Medicine, Stony Brook University, Stony Brook, New York,
7. Strategic Solutions, Inc., Cody, Wyoming,
8. Department of Physical Therapy, Winston-Salem State University, Winston-Salem, North Carolina,
9. Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina,
10. Department of Internal Medicine and Section on Infectious Diseases, Wake Forest School of Medicine, Winston-Salem, North Carolina,
11. GRECC Durham VA Medical Center, Duke University Medical Center, Durham, North Carolina,
12. Department of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Nashville, Tennessee,
13. Center for Wound Healing and Tissue Regeneration, University of Illinois at Chicago, Chicago, Illinois,
14. Burn and Shock Trauma Research Institute, Department of Surgery, Loyola University Chicago, Chicago, Illinois,
15. Department of Dermatology, Boston University School of Medicine, Boston, Massachusetts,
16. Department of Geriatrics, Baylor College of Medicine, Houston, Texas,
17. St. Luke's Wound Center, The Woodlands, Texas,
18. College of Nursing, University of Iowa, Iowa City, Iowa,
19. Penn Institute for Immunology, University of Pennsylvania, Philadelphia, Pennsylvania,
20. Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania,
21. Department of Dermatology and Cutaneous Surgery, Miller School of Medicine, University of Miami, Miami, Florida,
22. Wound Healing and Regenerative Medicine Research Program, Miller School of Medicine, University of Miami, Miami, Florida,
23. Division of Gerontology and Geriatric Medicine, University of Washington, Seattle, Washington,
24. School of Nursing, University of Washington, Seattle, Washington,
25. Department of Geriatrics, University of Arkansas for the Medical Sciences, Little Rock, Arkansas,
26. School of Physical Therapy, Western University, London, Ontario, Canada,
27. Smith & Nephew, Fort Worth, Texas, and
28. Association of Specialty Professors, Alexandria, Virginia

ARB	Angiotensin receptor blocker	MMP	Matrix metalloproteinase
BMDAC	Bone marrow–derived angiogenic cell	NPWT	Negative pressure wound therapy
DFU	Diabetic foot ulcer	PCR	Polymerase chain reaction
ECM	Extracellular matrix	PU	Pressure ulcer
FDA	US Food and Drug Administration	QOL	Quality of life
HIF1	Hypoxia-inducible factor 1	TGF-β	Transforming growth factor beta
LEA	Lower-extremity amputation	VLU	Venous leg ulcer

Reprint requests:
Dr. Lisa Gould, Wound Recovery and Hyperbaric Medicine Center, Kent Hospital, Warwick, RI 02886, USA.
Tel: 401 736 4646;
Fax: 401 736 4248;

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ABSTRACT

The incidence of chronic wounds is increased among older adults, and the impact of chronic wounds on quality of life is particularly profound in this population. It is well established that wound healing slows with age. However, 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 impact of age and accompanying multi-morbidity 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 paper, to explore the current state of knowledge and research challenges, engage investigators across disciplines, and identify key research questions to guide future study of age-associated changes in chronic wound healing.

Chronic wounds, which include venous leg ulcers (VLUs), diabetic foot ulcers (DFUs), arterial insufficiency, and pressure ulcers (PUs), disproportionately afflict 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 individuals, including vascular disease, venous insufficiency, unrelieved pressure, or diabetes mellitus. In addition, a disproportionate and increasing number of older adults undergo surgery and are at risk for wound complications. Fundamental questions remain about the impact 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. However, with better scientific and clinical tools, along with an increasing number of highly motivated and talented investigators, we are reaching a critical juncture to address these issues.

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, as well as 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 key epidemiologic, 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 epidemiologic 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 across 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 higher, and PU incidence five to seven times higher, in persons older than 80 years compared with persons aged 65 to 70 years.[1,2] Care for chronic wounds costs about $10 billion annually,[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 by generic and wound-specific instruments or by health utility.[4–6] The impact is similar to that seen with kidney or heart failure, and QOL decline is particularly precipitous among older adults. However, overall QOL among older populations with chronic wounds is poorly understood. Existing measures do not differentiate age-related differences in the impact of chronic wounds between community-dwelling older adults and those in long-term care. Data from the US Wound Registry indicate that patients in outpatient wound centers have an average of eight comorbid conditions.[7] However, there is no clear distinction between the QOL impact associated with chronic wounds and that associated with comorbidities.[8,9] Furthermore, QOL as a function of wound severity, etiology, and complications is poorly understood.

Although chronic wounds are cross-cultural, racial and ethnic disparities appear in wound severity at presentation and in subsequent treatment of wounds. However, these disparities are more likely to reflect socioeconomic differences and clinician bias. PU incidence among African American nursing home residents is more than 1.5 times that of white residents.[10–13] That disparity likely arises from differences in diagnosis and care; PU incidence increases among white residents who live in nursing homes where the majority of residents are African American.[10–13] LEA risk is also higher among African American and Native American patients, compared with non-Hispanic white patients, and it varies by culture among Hispanic patients.[14–16] However, the incidence of diabetes is also higher among nonwhite individuals, and

Table 1. Research questions for wound healing in older adults

Category	Research questions
Epidemiology and quality of life	1. What is the burden of illness due to chronic wounds in populations of older adults? 2. What is the frequency of multiple wounds and recurrent wounds in older adults? 3. What is the reason for racial and ethnic disparities in prevention and management of chronic wounds in older adults? 4. What is the impact of wound-associated pain on quality of life and function? 5. What are the effects of other comorbidities in conjunction with chronic wounds, with respect to quality of life? 6. What are the effects of socioeconomic status, living status, and other social factors on chronic wounds and quality of life? 7. How does adhering to evidence-based clinical guidelines affect complications and quality of life? 8. Does healing a chronic wound necessarily improve quality of health? 9. What is the impact of treatment regimens or evidence-based guidelines for chronic wounds on quality of life?
Basic biology of wound healing, chronic wounds, and aging	1. What causes acute injuries to become chronic wounds? 2. How can immune cells in the wound environment, or recruitment of immune cells to the wound, be modulated to harness benefit? 3. What strategies can be used to reverse macrophage impairment? 4. What factors regulate or activate macrophage phenotype in wound repair? 5. What are the mechanisms underlying endothelial and epidermal stem cell activation and homing to the wound site? 6. What are the roles of proliferation and apoptosis in acute vs. chronic wounds? 7. What are reasons for delayed chemotaxis and decreased neutrophil function in chronic wounds? 8. How does neutrophil depletion delay wound closure with advanced age? 9. What are the mechanisms for MMP overproduction with aging in chronic wounds? 10. What drives the changing composition and properties of ECM during development and aging? 11. What are the relative contributions of aging and comorbidities to the development of chronic wounds?
Molecular and cellular processes: inflammation	1. What mechanisms contribute to reduced HIF1α expression? 2. Does aging alter TGF-β signaling in chronic wounds? 3. How important are changes in inflammatory responses to age-related changes in wound healing? 4. How does inflammation affect the wound healing process in older adults? 5. What is the optimal inflammatory response that will support rapid repair, yet effectively reduce infection? 6. Can chronic wounds be forced to heal by manipulating inflammation alone?
Molecular and cellular processes: oxidative stress	1. What is the role of specific mitochondrial DNA damage in impaired skin healing?
Molecular and cellular processes: microbial burden	1. Which microbiota are beneficial, and which are problematic for wound healing? 2. How are systemic and local immune responses influenced by microbial bioburden in the wound? 3. How does age influence microbial burden in wounds and subsequent wound healing?
Clinical care: general	1. What is the clinical significance of delayed wound healing in older adults? 2. What is the significance of delayed wound healing from the patient's point of view? 3. Should wound care guidelines differ for older adults, accounting for heterogeneity and quality of life?
Clinical care: novel therapeutic approaches	1. What interventions effectively improve microcirculation and wound healing with aging? 2. What is the impact of wound therapies on universal patient outcomes, such as functional status, pain, physical impairment, mobility, and cognitive impairment, as opposed to wound-specific outcomes? 3. What is the effect of multi-component interventions on patient- and wound-specific outcomes? 4. Are there special considerations related to older patients with chronic wounds and dementia? 5. During surgery, what steps can anesthesiologists take to mitigate risk for chronic or nonhealing wounds? 6. How do various wound treatments affect microbial burden? 7. What new therapeutics can be developed based on the microbiome? 8. How should cellular therapy be positioned in wound care? 9. What potency assays are available to regulate cellular therapies? 10. What is the effectiveness of physical modalities such as electrical stimulation and ultrasound in older adults? 11. What is the impact of exercise on wound healing? 12. What interventions effectively prevent chronic wounds in older adults?
Clinical care: nutrition	1. Can patients be better categorized on the spectrum from cachexia to starvation, and can this categorization aid in determining the most effective nutritional treatment strategies? 2. What is the optimal protein and energy intake for older adults with chronic wounds, especially at weight extremes? 3. Is there a role for complete and various modular nutritional supplements and vitamin and mineral supplementation above the US recommended daily intake, or appetite stimulants and anabolic steroids in the care of patients with chronic wounds? 4. Are complete or modular commercial nutritional supplements better than regular foods?

ECM, extracellular matrix; H1F1, hypoxia-inducible factor 1; MMP, matrix metalloproteinase; TGF-β, transforming growth factor beta.

race and ethnicity are less of a predictor for LEA than other factors, such as differences in rates of peripheral vascular disease or smoking. Time to amputation is shorter for African American patients than for whites, but this disparity might also arise from differences in prevention and care: African American patients tend to receive less preventive care, while white patients 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, including inflammation, proliferation, angiogenesis, epidermal restoration, and wound contraction and remodeling.[20] Important cell types in this process include 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 show morphology similar to that seen in senescent cells. Fibroblasts from chronic VLU, particularly ulcers of long duration, show poorer responses to platelet-derived growth factor,[22] alterations in transforming growth factor beta (TFG-β) and TGF-β type II receptor expression,[23] and abnormal phosphorylation of key signal transduction proteins.[24] Decreased 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 is also 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 (HIF1) expression, fewer bone marrow–derived angiogenic cells (BMDACs), and dampened response and homing among BMDACs that are present (Figure 1).[25,26] Aging is also 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 change 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 shows considerable atrophy and a prolonged and blunted healing response[28] with heightened inflammation and differences in signal transduction, which result in inferior ECM production. Healing in older animals also involves a protective and noninflammatory response characterized by reduced matrix molecule production and reduced 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 increased in older human adults.[30] Age-related changes in hormonal status affect repair. MMPs, particularly

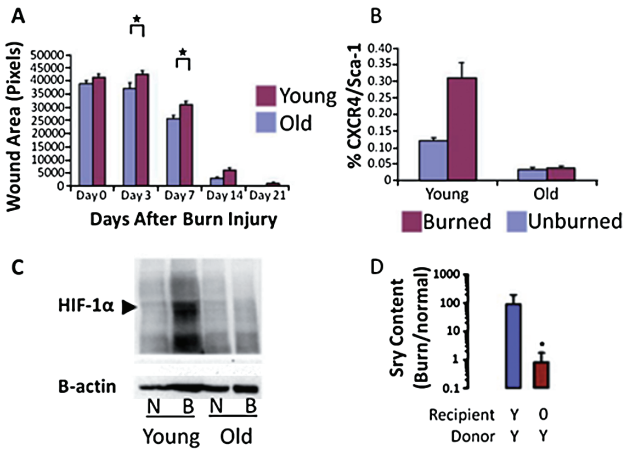

Figure 1. Burn wound repair is delayed in aged mice. (A) Wound area was evaluated 0, 3, 7, 14. and 21 days following burn injury in 2-month-old (young) vs. 2-year-old C57BL/6J mice (*$p < 0.05$). (B) Bone marrow–derived angiogenic cells were identified by fluorescence activated cell sorting as CXCR4+/Sca-1+. (C) Hypoxia-inducible factor 1 (HIF1) concentrations in response to burn injury are reduced in aged mice, compared with younger ones. (D) Bone marrow–derived angiogenic cells transferred from young male mice show impaired homing in older recipient mice, compared with younger ones (*$p < 0.01$ vs. young recipients by two-way ANOVA with Bonferroni post hoc comparisons). Donor cells were identified using the *Sry* gene as a marker. N, normal; B, burned.
Adapted from: Zhang et al.[25]

MMP2, are elevated principally in older postmenopausal females, and estrogen replacement therapy can stimulate the migration and proliferation of keratinocytes and elaboration of matrix.[30]

The microcirculation, defined as arterioles, capillaries, and venules, plays a critical role in wound healing. The microcirculation of aged skin shows impaired vasoregulation, which reflects changes in inflammatory responses, lower numbers of progenitor cells, and declines in circulatory mediators.[31] Age-associated delays in microvascular responses to stressors lead to impaired temperature regulation and increased likelihood of tissue hypoperfusion[31] that inhibits wounds from reaching the angiogenic stage of repair. Optimal healing strategies following surgery and other stressors must therefore use multifactorial approaches to address changes in the microcirculation in the older host. Potential strategies include better use of existing vessels to optimize vasodilation (e.g., physical activity, pneumatic compression, or pharmacologic 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 ECM.[37,38]

Molecular and cellular processes in wound healing

Inflammation

Under normal wound healing conditions, early macrophages promote inflammation, and later macrophages clear neutro-

Table 2. Properties in cutaneous ECM and wound healing across the life span[27]

Age of skin	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 a compliant ECM
Early adult	• Scarring properties at maximum • High production of type I collagen • Fibrotic response in a stiff ECM
Aged adult	• Prolonged inflammation • Increased MMP and elastase expression • Lower expression of TGF-β • Weakened cellular response in an atrophic ECM

ECM, extracellular matrix; MMP, matrix metalloproteinase; TGF-β, transforming growth factor beta.

phils and switch to a reparative phenotype. In the wounds of diabetic mice, however, macrophages fail to clear dying neutrophils and therefore remain in a proinflammatory phenotype.[39] Similarly, in both humans and mice, VLU 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 clearly 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 increased 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 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 occurs even in healthy individuals. Age-associated inflammation and delays in wound healing may have particular consequences for infection. In a mouse model inoculated with *Staphylococcus aureus*, older mice fail to clear the infection (Figure 2) and show less neutrophil chemotaxis, increased bacterial colonization, and slowed macrophage infiltration.[46]

Age-associated inflammation is characterized by sustained elevations in proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor alpha, and by declines in growth factors that are important for wound healing. TGF-β, which remains elevated 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] TGF-β expression is influenced by angiotensin receptor signaling. With diabetes or age, skin shows increased expression of angiotensin II and the proinflammatory, vasoconstrictive angiotensin 1 receptor signaling pathway.[48–50] Treatment with the angiotensin receptor blocker (ARB) losartan improves muscle remodeling after injury,[51] and diabetic individuals taking ARBs are less likely to undergo amputation, compared with those taking angiotensin-converting enzyme inhibitors.[52] Thus, angiotensin receptor signaling likely 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 HIF1α pathway.[53] Because of the high energy needs during wound repair and to avoid the overuse of mitochondria as the sole energy source, the process for adenosine triphosphate (ATP) generation shifts from oxidative phosphorylation to glycolysis. Although glycolysis is less efficient, it likely protects the mitochondrial pool from increasing damage related to oxidative stress damage.[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, which likely lead to dysfunctional mitochondria, decreased ATP pro-

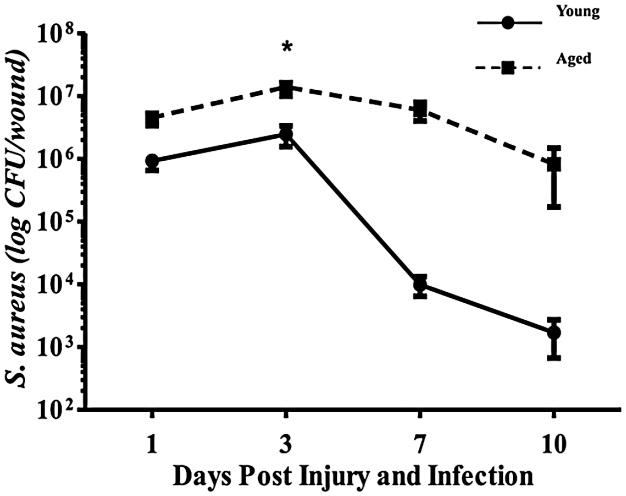

Figure 2. Implications of age-associated inflammation for infection. In a mouse model, older mice inoculated with *Staphylococcus aureus* fail to clear infection, compared with younger mice (*$p < 0.001$, two-way ANOVA).
Source: Brubaker et al.[46]

duction, and increased oxidative damage that triggers mitochondrial turnover. Skin mitochondria, particularly in exposed skin, show increased incidence of mitochondrial DNA 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] However, the link between age-associated mitochondrial dysfunction and impaired wound healing is poorly studied.

Microbial burden

The impact of microbial burden on wound healing is unknown and likely 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 RNA-based gene sequencing and quantitative polymerase chain reaction (PCR) have revealed that the skin and wounds have rich microbiomes with marked variability across body regions, 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 in DFU suggests 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. Among 30 patients with open fractures related to traumatic injury, bacterial community structure differs between patients who later develop complications and those who do not, as well as between upper- and lower-extremity wounds.[60] Further study with genomic sequencing techniques and clinical correlations might therefore identify microbial burden associated with the development of chronic wounds. The best collection methods are still unknown, however, and more standardization is needed to facilitate comparisons across 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 as the use of time-lapse photography to measure wound parameters, are available. However, 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 use of stem cells is hampered by concerns about immunogenicity, teratomas and other malignancies, the ability to maintain pluripotency, and limited supply. The use of embryonic stem cells is also hampered by 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. However, skin morphology and the mechanisms of wound repair differ markedly between mice and humans. Pig skin is closest to human skin,[61] but the utility of pig models is limited by a long life span and higher maintenance costs. 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.

The identification of predictive, diagnostic, and/or indicative biomarkers for wound healing has been difficult because of the multifactorial pathogenesis and the heterogeneity of sampling spanning across and within wound type. Very little is known regarding the contribution of aging in the context of specific biomarkers among older adults. Gene expression profiles have been identified in biopsies from VLU, DFU, or other chronic wounds, yielding a large number of potential biomarkers of nonhealing wounds.[62–65] However, the correlations of these tissue-based markers with wound healing outcomes and how to harness this information into predictive and diagnostic tools are not clear. Rapid tests that detect increased MMP levels in wounds can identify a subset of patients with poor wound healing,[66–70] but these tests are hampered by variability in obtaining and measuring specimens. It is still not clear which of these patients might heal with standard of care, whether observed differences represent cause or effect, or how age influences such tests. Furthermore, PCR-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 both 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 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 VLU, with the odds of wound healing being 2.75 times greater for patients with HP802-247, compared with those receiving the vehicle control.[73,75] Confirmatory Phase 3 clinical trials are underway in both the United States and Europe. In general, development of evidence-based clinical protocols for the therapeutic use of cellular and tissue-engineered approaches has been challenged by 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. Such development also has been hampered by the need for better defined regulatory and reimbursement pathways. Additionally, the

potential influences of patient age on cellular and tissue-engineered products are poorly characterized.

Negative pressure wound therapy

Although data from randomized controlled trials and meta-analyses suggest that negative pressure wound therapy (NPWT) 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 NPWT is poorly understood. Primary effects may include macro-deformation, or wound contraction, and micro-deformation, or the microscopic interaction between the wound and dressing. Potential secondary effects include increased 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 both chronological and replicative aging, resulting in poorer differentiation[95–97] and reduced mobilization.[98–100] However, 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 in patients of all ages has found that it effectively promotes wound closure.[102] Electrotherapy improves blood flow and prevents PU in a population affected by spinal cord injury,[103] and it may improve take of grafts and flaps, improve vascularization, reduce necrosis, and increase angiogenesis in patients with VLU or critical limb ischemia.[104–106]

Ultrasound

Low-frequency (22.5 to 35 kHz) ultrasound applied in contact rapidly debrides the wound surface and is a fairly comfortable procedure;[107] many patients 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, compared with antibiotics alone.[108–111] Low-frequency ultrasound also reduces antimicrobial resistance in vitro.[111] Data from a small clinical study among 17 patients aged 32 to 83 years with ulcers of mixed etiologies suggest that low-frequency ultrasound promotes healing for 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 underway in Canada (NCT01973361) and Australia,[112] but additional large, multicenter trials are needed.

Nutrition

Older adults categorized as undernourished are at increased risk for developing PU and other complex wounds.[113,114] However, this association may be confounded by factors other than inadequate nutrient intake.[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 impact 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 an adequate energy intake.[117] Recognizing that protein requirements are influenced by inflammation, the adequacy of energy intake, and other stressors common in older patients with complex wounds, the Agency for Healthcare Research and Quality developed recommendations for protein intake for patients with uncomplicated PU, but these estimates are based on anecdotal evidence.[117,118] There is conflicting evidence that dietary interventions or commercial supplementation is effective in preventing PUs or in 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. However, disentangling nutritional needs from all other factors affecting host 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. However, 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. Such a definition has been hindered by variations in data collection and in the definition, measurement, and treatment of wounds in older adults. Measurable outcomes also must be defined and several have been suggested (Table 3). A well-structured electronic medical record that follows the patient through the continuum of care will facilitate the measurement of these variables for clinical outcomes and research.

Approval of products or devices by the US Food and Drug Administration (FDA) is a major driver in the design and conduct of clinical trials.[126] However, the approval process in general is long and expensive, and only 1 in 25 products are eventually approved. Approval is even more constrained for wound care. Only three products for wound care have been approved by the FDA in the past 20 years,[127] and the FDA has defined only one endpoint—complete healing—for wounds.

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 vs. healing

Thus, traditional, FDA-driven, randomized trials, while 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 issue in clinical trial design for older adults centers on 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 among patients receiving standard care for DFU.[129] Another study has found that the area and duration of the wound, but not age, influence healing of VLU following spray therapy.[130] Thus, age does not appear to be a significant factor in the response to wound healing treatment. It can be an important predictor, however, as illustrated by the formula derived from a clinical database for an Ulcerated Leg Severity Assessment.[131]

UNANSWERED QUESTIONS, FUTURE DIRECTIONS, AND RESEARCH CHALLENGES

Future research will require common definitions and standardized procedures for data collection, and it 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 patient-centered measures, particularly those of most value to the patient, are also needed. With better measures and more data, additional endpoints might be accepted by the FDA for clinical trials in wound care, particularly in older adults. Common comorbidities are a major concern in the field of geriatrics and therefore should be explored both in clinical trials and in basic and preclinical studies. Issues related to polypharmacy should also 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. In addition, investigators studying wound healing can learn from other fields, such as cancer, 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-discipline educational approaches.

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Conflicts of Interest: Dr. Gould reports nonfinancial support from MiMedx, Cytomedix, Celleration, and Cardinal Health. Dr. Abadir has a patent: Novel, protective, anti-inflammatory receptor and its use in preservation of mitochondrial function, wound healing and repair pending. Dr. Davidson reports grants from National Institutes of Health and the Department of Veterans Affairs. Dr. Fife is the executive director of The Chronic Disease Registry (d/b/a the US Wound Registry [USWR]), a 501C(3) organization that provided some of the data for this presentation, specifically the data on the use of biological dressings among older patients and their associated healing rates. Dr. Grice reports grants from Janssen Research and Development; personal fees from GOJO, Amway International, GlaxoSmithKline, and L'Oreal. Dr. High reports grants from Chimerix, Sanofi-Pasteur,

Table 4. Available or forthcoming resources

Resource	Purpose
Infrastructure, databases, and registries	
US 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 • SF-36 • Sickness Impact Profile	Generic quality of life instruments
• Cardiff Wound Impact Schedule • Freiburg Life Quality Assessment	Wound-specific quality of life instruments
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

EQ-5D, EuroQol; SF-36, 36-Item Short Form Health Survey.

Optimer, and Astellas, other financial or material support from McGraw-Hill Publishers and Up-to-date, Inc., and is a consultant for University of Virginia and the University of Minnesota. Dr. Jacobson is a Smith and Nephew employee, which produces the cell therapy product described in the presentation. Dr. McFarland Horne reports grants from John A. Hartford Foundation during the conduct of the study. Dr. Tomic-Canic reports grants from NIH, Organogenesis Inc, Novan, and Smith & Nephew and is a scientific board member for Molnlycke. In addition, Dr. Tomic-Canic has the following patents: Methods and compositions for promoting wound healing issued to Hospital for Special Surgery; GM-CSF ceosmeceutical compositions and methods of use thereof issued to NYU School of Medicine; Biological markers of chronic wound tissue and methods of using for criteria in surgical debridement pending to NYU School of Medicine; Denovo synthesis of glucocortocoid in the epidermis and it uses and applications patent pending to NYU School of Medicine; and Growth factor mediated cosmeceuticals and use of thereof to enhances skin quality patent pending to NYU School of Medicine. H. Brem, M. Carter, T. Conner-Kerr, L. DiPietro, V. Falanga, S. Gardner, J. Harmon, W.R. Hazzard, P. Houghton, R.S. Kirsner, E.J. Kovacs, D. Margolis, M.J. Reed, K. Schmader, D.H. Sullivan, S. Thom, J. Walston, J. Whitney, J. Williams, and S. Zieman report no conflicts to disclose.

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