Exercise, Obesity, and Cutaneous Wound Healing: Evidence from Rodent and Human Studies

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Significance: Impaired cutaneous wound healing is a major health concern. Obesity has been shown in a number of studies to impair wound healing, and chronic nonhealing wounds in obesity and diabetes are a major cause of limb amputations in the United States.

Recent Advances: Recent evidence indicates that aberrant wound site inflammation may be an underlying cause for delayed healing. Obesity, diabetes, and other conditions such as stress and aging can result in a chronic low-level inflammatory state, thereby potentially affecting wound healing negatively.

Critical Issues: Interventions which can speed the healing rate in individuals with slowly healing or nonhealing wounds are of critical importance. Recently, physical exercise training has been shown to speed healing in both aged and obese mice and in older adults. Exercise is a relatively low-cost intervention strategy which may be able to be used clinically to prevent or treat impairments in the wound-healing process.

Future Directions: Little is known about the mechanisms by which exercise speeds healing. Future translational studies should address potential mechanisms for these exercise effects. Additionally, clinical studies in obese humans are necessary to determine if findings in obese rodent models translate to the human population.

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Abbreviations and Acronyms

EC = endothelial cell
ECM = extracellular matrix
GC = glucocorticoid
IGF = insulin-like growth factor
IL = interleukin
MCP = monocyte chemoattractant protein
MIP = macrophage inflammatory protein
MMP = matrix metalloproteinase
OVX = ovariectomized
PDGF = platelet-derived growth factor
PMN = polymorphonuclear leukocyte, neutrophil
TGF = transforming growth factor
TIMP = tissue inhibitor of metalloproteinases
TNF = tumor necrosis factor

SCOPE AND SIGNIFICANCE

This review is intended to highlight recent advancements in knowledge in the field of wound healing, obesity, and exercise, many of which are derived from rodent studies. The review focuses on the impact of obesity on wound healing, especially in the area of inflammation, as well as the role of exercise in speeding the healing process. Hypotheses concerning mechanisms by which exercise speeds healing are also included, and the review concludes with suggestions for future research directions.

TRANSLATIONAL RELEVANCE

Recent research has focused on the mechanisms by which obesity can delay healing. Among these, inflammation has been shown in many studies to play a major role. The evidence for this is discussed in some detail in this review. Additionally, there is now some interest in the impact of exercise on the healing of cutaneous wounds. Elucidation of the mechanisms by which obesity impairs healing, and the potential mechanisms by which exercise may ameliorate this process, will allow for intelligent choices of interventions which speed the healing process in obese individuals.

CLINICAL RELEVANCE

Obesity has a major detrimental impact on the wound-healing process.

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Interventions which ameliorate this effect are of particular interest. Research in our laboratory has focused on a short-term exercise paradigm which may be useful as a prescribed exercise intervention in obese individuals undergoing surgery, such as laproscopy. As surgical procedures create a cutaneous wound that heals more slowly in obese individuals, such exercise therapies may be beneficial for use in both prehabilitative and rehabilitative interventions. The exercise strategy employed in our studies is outlined in this review.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Wound healing

The process by which cutaneous wounds heal can be broken down into discrete phases. Despite some disagreement in the literature, wound healing can be thought of as consisting of four sequential and overlapping components. These are, in temporal order, hemostasis, inflammation, proliferation, and tissue remodeling/resolution.[1,2] Alterations in one or more of these phases can result in delayed healing, increased pain and risk of infection, and decreased quality of life for the wounded individual. In certain circumstances, chronic wounds develop in which the wound site does not heal or heals very slowly (> 8 weeks). This is common in type 2 diabetics[3] and is a major contributor to the majority of amputations performed in the United States each year. The molecular events in each of these phases are outlined below, and temporal regulation of normal healing is shown in Fig. 1.

Hemostasis. The initial phase of wound healing involves a rapid hemostasis which commences immediately after wounding.[1] Vascular constriction and fibrin clot formation reduce blood supply to the wound to prevent blood loss from hemorrhage. Growth factors and cytokines are then released from resident cells in the wound microenvironment. These factors induce the migration of leukocytes into the wound tissue, which results in a proinflammatory state.[1]

Inflammation. The earliest invading leukocytes are neutrophils (polymorphonuclear cells, PMNs), which are responsible for removal of cellular debris from the wounding process and for clearance of microbial pathogens from the wound microenvironment through phagocytosis, thereby lessening the risk of infection. Within a period of 1–2 days after wounding, activated neutrophils undergo apoptosis, allowing for their removal by macrophages.[4] This process both minimizes the bystander damage that can be caused by activated neutrophils and lessens the risk of the spread of infections which may occur as a result of pathogens

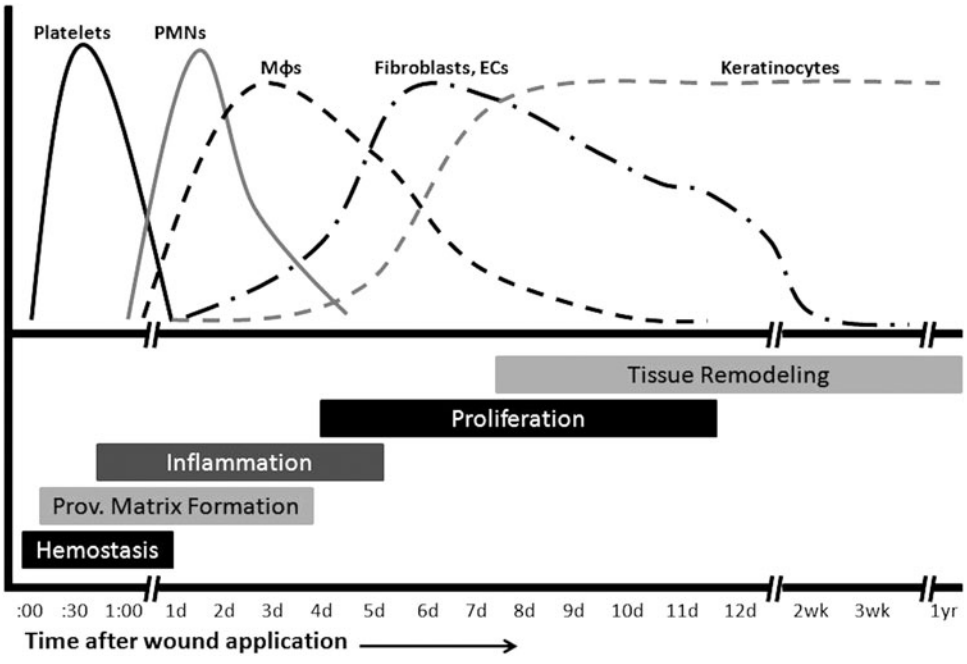

Figure 1. Phases of wound healing. (*Top*) Kinetics of cellular migration during normal wound healing. (*Bottom*) Time course of phases of wound healing. EC, endothelial cell; MΦ, macrophage. PMN, polymorphonuclear leukocyte (neutrophil).

(mainly bacterial) which can infect and propagate in phagocytic immune cells.[5]

In addition to neutrophils, macrophages play an important role in the wound- healing process. Resident macrophages in the tissue surrounding the wound site play an early role in the release of cytokines and growth factors which can attract other wound cells (including PMNs and emigrating monocytes) to the wound tissue.[1] At 2–3 days postwounding, invading monocytes from the blood differentiate into macrophages and allow for additional inflammatory processes to occur.[6] Macrophages, similar to PMNs, participate in the removal of microbial pathogens and the generation of antimicrobial reactive oxygen species, such as nitric oxide and peroxide.[2] Macrophage-assisted wound debridement occurs via the production of collagenase, elastase, and other enzymes which digest damaged tissue to allow wound healing to take place.[2] Production of cytokines and growth factors by macrophages are important regulators of chemotaxis of fibroblasts and endothelial cells (ECs),[7] both of which are imperative for the proliferative and remodeling phases of healing. Thus, macrophages play an integral role in promoting angiogenesis and extracellular matrix (ECM) synthesis in addition to their proinflammatory roles in the healing process. Indeed, treatment of rats with a monoclonal antibody against macrophages reduces wound-breaking strength and collagen deposition in wounds.[6]

Apoptotic neutrophils are phagocytized by macrophages in a process known as efferocytosis. Efferocytosis allows, by a mechanism that has not yet been well-defined, for a phenotypic switch in macrophages from a pro- to an anti-inflammatory state.[8] This switch helps to reduce inflammation in the wound tissue thereby paving the way for transition to the later phases of healing. Thus, the phagocytosis of neutrophils by macrophages causes the resolution of the inflammatory phase of healing and allows the proliferative and tissue remodeling phases of healing to proceed.

Other immune cells, including various populations of T lymphocytes, play an important role in the healing process, especially late in the inflammatory and early in the proliferative phase. Readers who desire more information on this may refer to an excellent review by Keen which covers this topic in-depth.[9]

Cytokines and growth factors released from both immune and nonimmune cells in the wound and surrounding tissues also play a major role in the process of healing, although their precise roles are sometimes debated. Cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, as well as growth factors, such as transforming growth factor (TGF)-α, TGF-β, platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF)-1, can stimulate angiogenesis and collagen synthesis in the wound microenvironment.[6] Most of these factors, with the exception of the ILs, also stimulate EC and fibroblast proliferation.[6] Some studies have shown different effects of these molecules on healing; suggesting that further work is needed to fully describe the roles of these proteins in the healing process. Studies in mice demonstrated that knockout of TNF-α promotes excessive granulation tissue formation and impairs re-epithelialization in cutaneous wounds,[10] while ablation of IL-1 signaling through knockout of the IL-1 receptor reduced fibrosis and improved tissue remodeling using a similar model.[11] Further, loss of granulocyte/macrophage colony–stimulating factor impaired healing and reduced cytokine production (including monocyte chemoattractant protein [MCP]-1 and IL-6) at the wound site.[12] Thus, while proinflammatory cytokine signaling is necessary in most cases for proper wound healing, aberrant inflammation can delay healing.

Proliferation and tissue remodeling. After the inflammatory phase of healing at about day 4–5 postwounding, robust proliferation of reparative cells occurs. Epithelial cells (keratinocytes) migrate to the wound site and proliferate in a process known as re-epithelialization.[13] A fibrin-rich provisional matrix allows for integrin-dependent keratinocyte migration and attachment in the wound. Basement membrane (types IV and VII) and interstitial (types I, III, and VI) collagens help anchor keratinocytes at the provisional matrix. During migration, keratinocytes secrete collagenases, including matrix metalloproteinase (MMP)–9, a process which is necessary to remove damaged tissue and provisional matrix and to allow for uninhibited migration in the wound site.

Fibroblasts and ECs in the dermal layer allow for collagen deposition and angiogenesis as well as for granulation tissue formation at the wound site.[1] ECs migrate and proliferate to form new blood vessels to allow for increased flow of oxygen and cells to the wound tissue.[14] This process is stimulated by the release of proangiogenic growth factors, including TGF-β, PDGF, and vascular endothelial growth factor, which induce proliferation and migration of ECs to the ECM where new vessels are formed. Similar to keratinocytes, ECs release proteolytic factors, including collagenases

to disrupt the ECM, allowing for migration into the wound area.[15]

Fibroblasts, induced by hypoxia in the wound tissue, migrate and release collagen, fibronectin, and other components of the ECM.[16] These ECM constituents form the granulation tissue that allows for keratinocyte and EC migration and provide strength and integrity to the wound. Apoptosis of fibroblasts occurs later in healing during the transition from the proliferation to remodeling phases and allows for final healing or scar formation to occur. Contraction of the wound site, a process which is thought to be induced by migration and activation of specialized fibroblasts, known as myofibroblasts, in the wound tissue, occurs throughout both proliferation and remodeling.[1,16] In the final phase of wound healing, new capillaries regress and ECM is remodeled such that the architecture of the wound site closely mimics that of normal tissue.

Alterations in wound healing. A number of factors can cause dysregulation of wound healing. At the systemic level, age, gender, hormone status, obesity, stress, medication use, alcoholism, smoking, poor diet, and immunocompromisecan delay or alter healing rate.[1] Altered inflammation is associated with delayed healing in aged populations,[17] and these alterations can result in reductions in angiogenesis and remodeling of the wound site in these groups. Interestingly, although inflammation in these individuals seems to be increased, macrophage function seems to be reduced,[18] suggesting that risk of infection may be increased in aged individuals despite their abnormally high levels of local tissue inflammation.

Use of anti-inflammatory medications, such as glucocorticoids (GCs), nonsteroidal anti-inflammatory drugs, and chemotherapeutics have been shown to slow healing, mostly as a result of interference with platelet function or inflammatory processes.[1] In addition, stress responses are well known to be detrimental to wound healing.[19] Chronic psychological stress, through the induction of GC expression, reduces expression of inflammatory mediators and chemokines in the wound tissue and can inhibit the influx of inflammatory cells, such as PMNs and macrophages into the wound environment,[20] thereby disrupting the repair process. However, acute stress can increase immune responses and may be potentially protective against delayed healing,[21] a finding which may parallel those seen in the exercise literature discussed below.

Finally, a major area of interest in the area of wound healing is that of the effects of obesity and diabetes on the healing process. In addition to the myriad of disease conditions to which obesity is related, obese persons are at greatly increased risk of wound infections, pressure, and venous ulcers, and delayed wound healing after major surgeries.[1,22] Thus, interventions which can combat these phenomena are of great interest to the medical community and are the focus of a number of current studies.

Obesity and wound healing

There is a wide body of literature demonstrating a link between obesity and a proinflammatory state. For a broad overview of this evidence, we refer the reader to a recent review by Kalupahana *et al.*,[23] which covers this topic in much more depth than is possible here. Because of the pivotal role that inflammation plays in healing, much of the work in this area has focused on the effects of inflammation on healing in obesity.

Early evidence indicated that diabetic foot ulcers, a type of chronic nonhealing wound that is responsible for most nontraumatic amputations,[24] were associated with an increase in wound-adjacent inflammatory cell accumulation in obese diabetic patients.[25] However, in diabetic patients, leukocyte function is impaired,[26] which can predispose such individuals to infection even in the presence of elevated wound inflammation. These studies provided evidence that aberrant inflammation in obesity and diabetes is associated with, and can be detected near, the site of impaired wound healing, paving the way for mechanistic studies using animal models of these conditions. In diabetic mice and humans, delayed wound healing is associated with decreases in most growth factors, including TGF-β, PDGF, and IGF-1, as well as increases in proinflammatory cytokines, such as TNF-α and IL-1β.[3] Additionally, impaired healing is associated with dysregulation of collagen turnover, including increased MMP and decreased tissue inhibitors of metalloproteinase (TIMP) activity as well as decreases in angiogenesis, granulation tissue formation, and collagen deposition.[3]

High-fat diet studies. Rats fed a high-fat diet consisting of 30% total kilocalories from fat for 15 weeks had significantly higher percentage of initial wound area remaining at 14 and 21 days post-wounding compared to nonobese control mice.[27] Re-epithelialization of the wound area was also impaired in high-fat diet-fed mice, and the control group showed greater fibroblast infiltration at 21

days postwounding compared to their obese counterparts. In a similar study, rats fed a high-fat diet for 4 months had reduced wound strength compared to nonobese controls in an experimental model of abdominal laparotomy, which induces a skin wound as well as scar formation.[28] In a study in female mice, those rodents fed a reduced-calorie diet healed faster than either ovariectomized (OVX) or intact mice fed a HFD, although presence of estrogen was partially protective against delayed wound healing, possibly as a result of increased weight gain in the OVX mice.[29]

Genetic obesity studies. In a comparative study, HFD-fed mice were tested alongside genetically-obese *ob*/*ob* mice to determine wound closure rates relative to nonobese controls. Although *ob*/*ob* mice gained much more weight than HFD-fed mice, both groups had greatly impaired wound healing relative to nonobese C57Bl/6 control mice.[30] In a model of diabetic foot ulcers, genetically obese *db*/*db* mice had greatly delayed healing compared to both +/+ and *db*/+ controls, with both nondiabetic strains having 100% wound closure at day 21 compared to 50% closure at the same time point in *db*/*db* mice.[31] Similarly, genetically obese Zucker rats had larger wound size and reduced wound strength in a model of laparotomy wound healing at 28 days postoperation.[32]

Mechanisms. In genetically-diabetic *db*/*db* mice, impaired wound healing is associated with increased and prolonged expression of inflammatory chemokines, including MCP-1 and macrophage inflammatory protein (MIP)-2, and expression of these chemokines results in increased levels of PMN and macrophage infiltration into the wound site.[33] Due to the leptin-resistant nature of *db*/*db* mice and the defects in wound healing seen in leptin-deficient *ob*/*ob* mice, Goren *et al.*[34] hypothesized that leptin plays a role in the inflammation-induced defects in healing seen in both types of genetically-obese mouse models. Administration of leptin to *ob*/*ob* mice sped healing, and was associated with a reduction of PMN but not macrophage infiltration into the wounds of the mice.[34] Additionally, leptin administration attenuated PMN-associated MIP-2 expression, with no change in MCP-1 expression. This suggests that, at least in a leptin-deficient model of obesity, PMNs play a larger role in healing response than do macrophages, especially at early time points, a finding that underscores the importance of proper resolution of inflammation in healing. This is supported by the finding the neutrophil depletion in diabetic mice sped healing,[35] evidence that PMNs may be important for pathogen defense in wounded tissue yet ultimately detrimental to the healing process in sterile wounds.

More recently, Goren *et al.* directly investigated the role of inflammation in delayed healing in *ob*/*ob* mice using neutralizing antibodies against TNF-α and F4/80, a macrophage cell surface protein, to dampen systemic inflammation in an attempt to speed healing.[36] Although these treatments did not reverse their symptoms of the metabolic syndrome, healing rate was markedly increased in the antibody-treated mice. Additionally, inflammation in these mice was decreased by antibody treatment, as mRNA levels of IL-1β, TNF-α, and COX-2 were reduced and numbers of circulating monocytes as well as numbers of wound-associated macrophages were also decreased. Likewise, TNF-α impairs insulin signaling in wounds in *ob*/*ob* mice[37] and increases fibroblast apoptosis at the wound site in *db*/*db* mice.[38]

Recent evidence has supported the hypothesis that leukocyte dysfunction mediates delayed healing in obesity and diabetes. Macrophages are responsible for clearing apoptotic PMNs from the wound site in order for healing to progress. However, an increase in apoptotic cells has been noted in both genetically-diabetic *db*/*db* mice as well as diabetic humans.[4] These apoptotic cells were shown to be PMNs, and wound-associated macrophages isolated from *db*/*db* mice were unable to clear apoptotic cells *in vitro*, suggesting that macrophage dysfunction can prolong the inflammatory state in diabetic wounds, as efferocytosis of apoptotic PMNs is potentially necessary for resolution of inflammation.[8]

Interestingly, a comparative study of genetically-diabetic and HFD-fed mouse models of obesity indicated that, while the genetically-obese *ob*/*ob* mice developed chronic wounds, HFD-fed obese mice did not develop chronic wounds, although healing was delayed in this model.[30] Therefore, while *ob*/*ob* and *db*/*db* mouse models are preferred for studies of healing mechanisms of chronic wounds, such as diabetic leg ulcers, wounds of HFD-fed mice may be much more suited to the study of delayed healing of acute wounds, such as those induced by bariatric or other surgeries in obese individuals.

Exercise and wound healing

In recent years, there have been numerous published studies examining the impact of various exercise modalities on inflammation in obesity. In general, studies demonstrate that exercise

training tends to reduce inflammation in obesity, whether humans or rodent models are utilized. For comprehensive treatment of this topic, we refer the reader to excellent review articles from 2001 in *Nature Reviews Immunology*[39] and *Exercise Immunology Review*.[40]

Given the significant effects of exercise on inflammation in obese individuals, both systemically and locally, a logical hypothesis would be that exercise training could reduce the aberrant inflammation seen in wound tissue in obese individuals and thereby ameliorate the delays in wound healing often seen in this population. However, to date only one published study,[41] from our laboratory, has examined the role of exercise on wound healing using an obesity model, either in humans or in experimental animals. A small number of additional studies have focused on the role of exercise in modulation of the wound-healing process using an aging model of delayed healing. As aged individuals exhibit chronically elevated inflammation similar to that seen in obese individuals,[42] findings from these studies are important data points by which to generate a working hypothesis for extension of these studies to an obesity model of wound healing.

In a study of older adults published by Emery in 2005,[43] cutaneous wounds were applied one month after onset of the exercise intervention. Wound healing was then assessed until total closure of the wound. Exercisers healed significantly faster than sedentary subjects (mean time to total closure 29 days vs. 39 days, respectively). No molecular measures of wound status were taken during the course of the study; thus, no real inferences can be drawn as to the mechanisms behind these changes. However, this study was the first to definitively show the effect of exercise on healing of cutaneous wounds.

A study from our laboratory, utilizing 40 aged mice randomized evenly into exercised and sedentary groups,[44] was performed to test the potential mechanisms by which exercise might speed healing in aged individuals. Similar to the Emery study referenced above,[43] it was found that exercise significantly sped healing compared to healing rate in sedentary controls. Interestingly, the major differences in healing rate between groups occurred early (1–5 days) postwounding, indicating that exercise may be exerting its effects on healing during this phase of healing. This corresponds with the inflammatory phase of healing as discussed previously. Thus, the investigators assessed the inflammatory status of the wound using gene and protein expression for selected proinflammatory cytokines and chemokines, comparing results for exercised and control mice. TNF-α wound protein expression was reduced with exercise at days 3 and 5 postwounding, with a nearly significant reduction at day 1 postwounding as well. Likewise, MCP-1 protein was reduced with exercise at days 1 and 3 postwounding, while keratinocyte chemoattractant protein, the mouse equivalent to the human neutrophil chemokine IL-8, was reduced with exercise at days 3 and 5 postwounding. However, there were no differences in F4/80 gene expression or in wound myeloperoxidase (MPO) activity, proxy measures for macrophage and neutrophil wound infiltration, respectively. Thus, the data from this study[44] suggests that exercise speeds wound healing rate in aged mice, and that this is associated with reduced inflammation despite no significant changes in inflammatory cell infiltration; although this was not assessed directly.

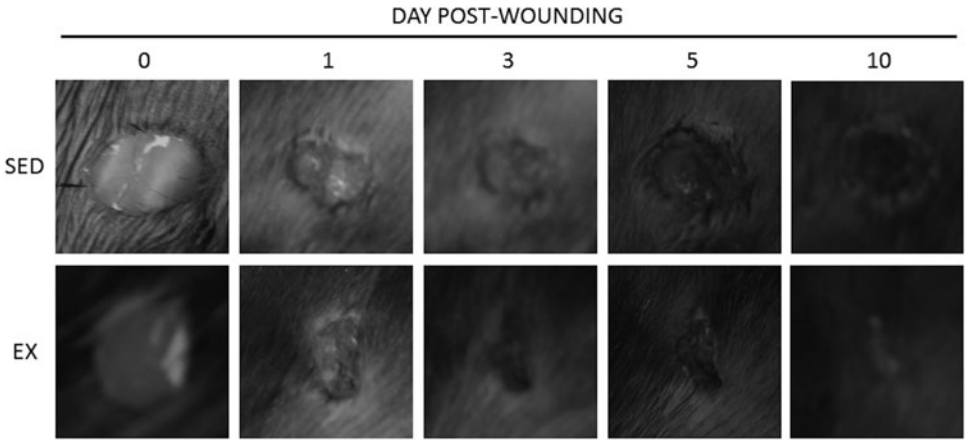

Figure 2. Example wounds from obese mice. SED, sedentary mice. EX, treadmill-exercised mice.

Additionally, we recently demonstrated that short-term exercise training can speed healing in obese, high-fat diet-fed mice.[41] As in Keylock *et al.*,[44] we found that the impact of exercise occurred early (within 5 days) postwounding when mice were exercised for 3 days before and 5 days postwounding. Representative wound images from this study are displayed in Fig. 2. However, unlike in the previous study with aged mice, we found no impact of exercise on gene or protein expression of either pro- or anti-inflammatory cytokines in the wound tissue of these obese mice. Likewise, we found no impact of exercise on the expression of chemokines regulating the migration of either macrophages or neutrophils. Our use of premenopausal female mice in this study may have played a role in our failure to demonstrate an effect of exercise on inflammation, as estrogen is known to play a protective role in this area.[29]

TAKE-HOME MESSAGES

- It is well established that conditions, such as obesity and aging can impair the normal wound-healing response, leaving the organism susceptible to infection, prolonged pain, and other complications.
- Recent evidence indicates that physical exercise may be able to speed cutaneous healing in both aged humans and in rodent models of both aging and obesity. However, the mechanisms by which exercise acts are not completely clear, as our lab has found differential effects of exercise on wound site inflammation in aged and obese mice.
- Future studies in this area must examine the impact of age, gender, and mouse strain to resolve some of these differences. Further research is also needed into mechanisms by which exercise acts to speed healing.
- Clinical research must be undertaken to apply these findings from rodent studies to human populations. The field of exercise and cutaneous wound healing research is still in its infancy, and many questions are still to be answered.

The results of the above studies shed light on potential mechanisms by which exercise might speed wound healing in obese individuals. The field of exercise research in cutaneous wound healing is in its infancy, and significant work remains to be done using obesity, aging, and other models of delayed healing. Interestingly, the Keylock *et al.* study discussed above[44] found a nearly significant effect ($p = 0.10$) of exercise on healing rate in young, healthy mice, suggesting that exercise might speed healing even in those without aberrant basal inflammation, although a mechanism by which this may occur is not clear at this time.

Limitations. The studies published by our lab[41,44] utilized a short-term exercise paradigm, shown in Fig. 3. The intent was to establish an exercise intervention that can be used clinically to speed healing of surgical wounds in obese individuals. However, currently there have been no studies examining such exercise interventions in humans. Additionally, it is possible that longer-term exercise may have differential effects both on healing rate and on wound site inflammation. Thus, more research is needed to determine both the impact of exercise on healing in obese adults and the optimal exercise paradigm by which accelerated healing can be accomplished.

Importantly, the mechanisms of normal healing differ between humans and mice. Skin architecture in mice is distinct from that of humans. In addition to the presence of hair covering much of the body, mice lack sweat glands and dermal papillae, both of which are present in humans.[45] Additionally, mice heal primarily through contraction of the wound site, while humans heal via granulation tissue formation and re-epithelialization as described

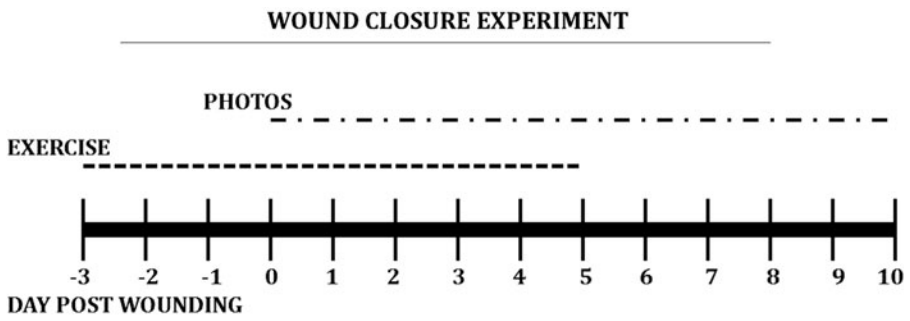

Figure 3. General wound healing study design from experiments in our laboratory. Mice undergo treadmill exercise for 30 min per day, starting 3 days before wounding and continuing daily until 5 days postwounding. Wound size is measured by photoplanimetry daily starting on the day of wounding and continuing until 10 days postwounding. For determination of wound site inflammation, wounds are harvested from mice at days 1, 3, and 5 postwounding.

above.[46] Thus, it is critical to understand the differences in healing mechanisms between organisms, as discoveries made using one species may not fully translate to wound healing strategies of another species.

AUTHOR DISCLOSURE AND GHOSTWRITING

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