Review Article

Delayed Wound Healing: Can Exercise Accelerate it?

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ABSTRACT

Int J Exerc Sci 3(3): 70-78, 2010. Poorly healing wounds affect millions around the world, yet preventive methods and low-cost, effective treatments are few. Wounds heal quickly through well-coordinated phases in those who are healthy and active but can become chronically non-healing as a result of disease and inactivity. Recently it has been reported that moderate aerobic exercise accelerated healing rates in the aged. High levels of inflammation are known to delay wound healing, and aging and disease are associated with chronically increased inflammation. Therefore, exercise may help speed healing by reducing inflammation to healthier levels not only in the aged, but also in other populations with increased inflammation. Further research is needed to better characterize the anti-inflammatory effects of exercise and specific mechanisms of accelerated wound healing.

KEY WORDS: wound healing, exercise, inflammation, short review

INTRODUCTION

Type 2 diabetes is on the rise around the world, and one of the main health concerns for this population is poorly healing wounds (see figure 1). Delayed and chronically non-healing wounds can result in increased pain, loss of mobility, and decreased productivity and quality of life. This is not only of interest to individuals with diabetes, but it also affects the financial health of the community in which they live. Chronic wounds affect millions of people worldwide, and in the United States alone the associated health care cost is $25 billion annually (36).

Since the number of people with delayed healing is growing rapidly, such as those with diabetes, obesity, and the aged, interventions are needed to quickly and economically treat this public health problem. One such intervention is regular aerobic exercise. However, to date very few studies have examined the impact of exercise on wound healing. This paper will review the evidence for the impact exercise can have on wound healing, especially in those with delayed healing, and will explore some potential ways by which exercise may improve healing rates.

Wound Healing Overview

Wound healing is a complex, well-coordinated process that includes the circulatory, immune, and endocrine systems. The phases of healing include hemostasis/coagulation, inflammation, proliferation, and remodeling. Progression

through the stages in a timely manner is critical to avoid chronic, non-healing wounds. A brief outline of the stages is presented here. For a more detailed description, there are many wound healing review articles available in the literature (3, 8, 26).

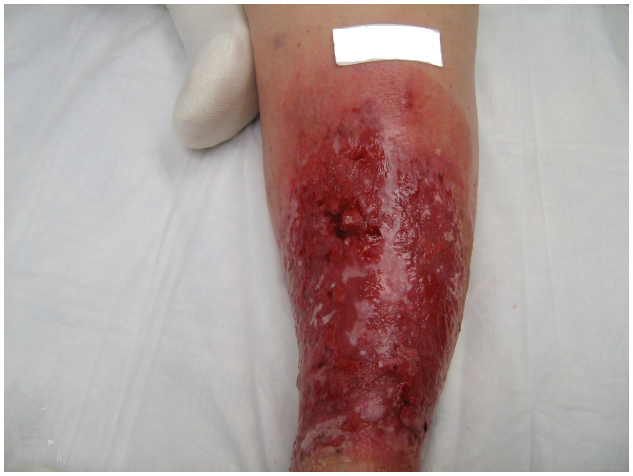

Figure 1. Chronic non-healing lower leg wound in 69-year-old pre-diabetic female. Used by permission.

Hemostasis

After an organism is wounded, the highest priority is to control bleeding. Therefore the first phase of wound healing is characterized by platelet degranulation leading to the formation of a thrombus (clot). When platelets are exposed to collagen and thrombin (released from intrinsic and extrinsic clotting cascades) they are activated and begin to aggregate. They secrete fibrinogen and fibronectin, which ultimately lead to the formation of a platelet plug. The matrix that results from this process serves as a pathway to help guide inflammatory cells that arrive soon afterwards into the wound site (26). Platelets also release many cytokines and growth factors, including platelet derived growth factor (PDGF), transforming growth factor alpha (TGF-α), transforming growth factor beta (TGF-β), and epidermal growth factor (EGF) (8). This leads to an inflammatory response which serves to clear away bacteria and other pathogens that have crossed the usually unbroken barrier of the skin.

Inflammation

Recruitment of polymorphonuclear lymphocytes (neutrophils) and macrophages are key events in the inflammatory stage. Neutrophils are recruited first, then macrophages. These cells are recruited by chemokines such as interleukin 1 beta (IL-1β), keratinocyte chemoattractant (KC), and monocyte chemotactic protein 1 (MCP-1). Chemokines upregulate adhesion molecules that facilitate the process of cells leaving the blood and entering the wound site by a process called diapedesis. They home in on the wounded area by following a concentration gradient of chemokines generated by cells at the wound site. Once there, neutrophils can begin to carry out their function of killing pathogens and clearing damaged and dead tissue. Neutrophils also generate enzymes and toxic oxygen molecules (reactive oxygen species) which are used to kill pathogens (8). This process goes on for several days, and it can be prolonged if significant amounts of bacteria have gotten into the wound environment. Once any pathogens have been removed, neutrophil recruitment to the wound site drops off and they are phagocytosed and eliminated by macrophages and fibroblasts.

As platelets and neutrophils begin to decline in number, monocytes circulating in the blood are drawn to the wound site where they mature into macrophages. This process begins within a day or two of wounding and can continue for weeks. Macrophages serve many roles in wound

healing, including killing of pathogens, phagocytosis, wound debridement, secretion of cytokines and growth factors, cell recruitment, and stimulation of angiogenesis (8). Among the many cytokines and growth factors produced by macrophages are IL-1, interleukin 6 (IL-6), PDGF, TGF-β, EGF, fibroblast growth factor (FGF), tumor necrosis factor alpha (TNF-α), and vascular endothelial growth factor (VEGF) (41). Since macrophages participate in both inflammation and wound repair, they are thought to play a role in the transition between the stages of inflammation and repair (8).

Proliferation

A main purpose of the proliferation phase of wound healing is for the skin to once again become a functional barrier. Keratinocytes and fibroblasts begin to proliferate, producing fibronectin and collagen, which lead to re-epithelialization of the wound (8). This temporary epithelium serves to keep out foreign substances like bacteria and will be replaced by a stronger epithelium during the remodeling phase. Three or four days after wounding, granulation tissue begins to form. This tissue is granular in appearance and is composed of macrophages, fibroblasts, and new blood vessel growth (8). Since blood supply to much of the wounded area has been cut off, growth of new blood vessels to deliver oxygen and nutrients is critical to rapid and effective healing. Several factors, including low oxygen and lactic acid, are potent stimulators of angiogenesis in this environment (26). This is also when wound contraction (the process of the wound getting smaller) is completed (see figure 2). Wound contraction occurs when fibroblasts undergo a phenotypic change to myofibroblasts, which contain contractile proteins.

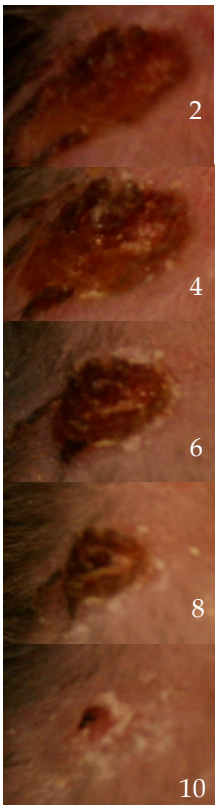

Figure 2. This figure shows representative pictures of wounds in diabetic mice healing over time. These photos were taken 2, 4, 6, 8, and 10 days after the wounding procedure was performed.

Remodeling

Finally, the long remodeling phase involves developing and remodeling the extracellular matrix for weeks and months. As the composition and structure of the extracellular matrix change, tensile strength increases, replacing fibronectin with type III collagen, which is then replaced with the more stable type I collagen (8). Remodeling and collagen turnover are tightly controlled by collagenases, matrix metalloproteinases, and tissue inhibitors of matrix metalloproteinases (TIMPs). Eventually the wounded area gets close to its pre-injury strength.

In the young and healthy, these overlapping stages proceed quickly and without complication. However, the wound

healing process can be delayed and disrupted in many people by aging and disease, creating a need for interventions to correct the delays.

AGENTS INFLUENCING HEALING

Many influences that delay wound healing have been evaluated, including medical (such as steroid medications), lifestyle (such as smoking), and biological (such as advanced age), but few have been found that can improve healing (20). Agents that improve healing include hyperbaric oxygen therapy (15), certain nutritional therapies (7), and estrogen (17). In terms of delayed wound healing, exercise has the potential to be both a preventive measure and a treatment when wounds become chronic. In addition, exercise is cost effective, avoids the side effects of most medications, and confers a host of other positive health benefits.

In 2005, Emery et al. published the first paper evaluating the effects of exercise in a population with delayed wound healing. In that study the subjects were healthy older adults (average age = 61) who exercised at a moderate intensity three days a week for a total of three months. Control subjects were asked to not change activity levels during that time. Wounds created in subjects in the exercise group healed (decreased to less than 10% original size) significantly faster (29 vs. 39 days) than those in the sedentary control group.

These results were similar to a study on the effects of exercise on wounds in older mice published in 2008 (25). Moderate aerobic exercise (~70% VO_2 max) was performed on a motorized treadmill by aged female mice (Balb/cByJ, 18 months old). Wounds in the exercised mice contracted at a faster rate than control mice and the pattern of healing was closer to that typically found in young mice (Figure 3).

It is well known that a sedentary lifestyle is

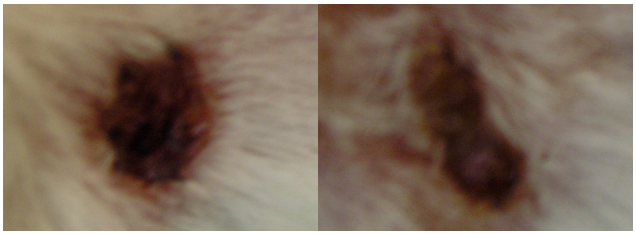

Figure 3. This figure shows a wound from a sedentary control mouse on the left and a wound from an exercised mouse on the right. Both photos were taken three days after the mice were wounded. The wound on the right has a smaller area due to faster wound contraction.

associated with many negative health consequences, including increased rates of obesity, diabetes, and heart disease. There is also evidence that lack of physical activity can impair healing. Two conditions that simulate being sedentary, mechanical unloading and microgravity support this claim. When rats' hindlimbs are suspended to simulate bed rest, not only do they experience muscle wasting and thinning bones, but wound healing patterns are also affected. Wound closure is delayed and the function of critical cell types such as keratinocytes and endothelial cells are impaired (33). Several phases of wound healing have also been reported to be disrupted under conditions of microgravity, as well as decreased production of growth factors and cytokines (12). Therefore, not only is exercise a positive stimulus for healing, but a decreased amount of exercise is a negative influence.

When hypothesizing about the mechanisms of accelerated healing from exercise, Emery et al. (10) suspected there may be an effect

of exercise on the inflammatory phase of wound healing. This suspicion was confirmed in a later study (25). When wounds in old mice were evaluated for inflammatory cytokines, the cytokines were lower in the exercised group. So what is the relationship of inflammation to healing?

INFLAMMATION AND WOUND HEALING

Inflammation is a critical part of many physiological processes and is an important part of wound healing. However, most of the literature agrees that lower levels of inflammation lead to faster and better wound healing (38). Most of the evidence comes from research on animals, where those with lower levels of inflammation have rapid and effective healing of wounds.

Three decades of research have established that wounds created in mouse fetuses, which exhibit low levels of inflammation, heal much faster than wounds in adult mice (for example, 27). When mice are bred to be deficient in specific cell types or cytokines (mutant or knockout mice) they can be used to evaluate the roles each cell or cytokine plays in the healing process. For example, PU.1 null mice lack macrophages and neutrophils and have greatly reduced levels of inflammation, but they heal faster than wild type mice (28).

On the other hand, in mice that have high levels of inflammation, such as mutant diabetic mice (C57BLKS/J-*m* +/+Lepr^{db} or *db/db*), wound healing is delayed and numbers of neutrophils and macrophages stay elevated much longer in the wound healing process when compared to wild type mice (42). By administering antibodies to neutralize several cytokines, researchers found that this elevation is a result of increased expression of chemoattractants such as MCP-1 beyond the usual time course of their expression in non-diabetic mice. The authors also found a prolonged inflammatory stage of healing measured by an elevation of TNF-α mRNA and IL-1β protein. These increases were seen as late as 13 days post wounding, but levels in control mice were dropping by day five. Therefore, a dysregulation in cytokines and chemokines related to inflammation may be an underlying cause for the delays in wound healing in these mice. In all these studies of wound healing, high levels of inflammation are associated with delayed healing, while low levels of inflammation lead to faster and better healing.

EXERCISE AND INFLAMMATION

There is an increasing amount of evidence demonstrating that regular physical activity and/or exercise may decrease levels of inflammatory markers in the blood. A few large epidemiological studies point to an inverse relationship between activity and inflammation, although no causal relationship can be claimed. For example, Ford (14) examined NHANES III data and found that the more active the subjects were, the less likely they were to have elevated levels of C-reactive protein (CRP), a common measure of systemic inflammation. Of the sedentary subjects, 21% had elevated CRP, where only 17% of lightly active, 13% of moderately active and 8% of vigorously active subjects did.

Many (but not all) studies show the effects of exercise on systemic inflammation in populations where inflammation tends to be high, such as in the aged. In men and women over 65, CRP and four other

markers of inflammation were lowest in the most active subjects (16). Colbert et al. (9) examined CRP and TNF-α in adults 70-79 years of age and found that higher levels of exercise were associated with lower levels of both markers of inflammation. In addition, among those who were considered non-exercisers, those who were more physically active also had lower levels of CRP (but not TNF-α). Heart rate recovery, a measure of fitness, has also been shown to be inversely correlated to CRP levels in older adults (40). In the DNASCO study (34), a six-year randomized trial in middle-aged Finnish men, the men assigned to the aerobic exercise group had consistently lower CRP levels at yearly intervals.

In other populations known to have elevated levels of inflammation, the effects of exercise have been similar (29). One such group is breast cancer survivors: 15 weeks of aerobic exercise decreased the levels of CRP in the serum, but it increased slightly in the control group over the same time period (11). Cadet et al. (6) found that Parkinson's patients had an increase in anti-inflammatory cytokines, such as IL-10, after regular exercise. Heart failure patients had a decrease in TNF-α and other pro-inflammatory cytokines after 12 weeks of exercise (1). In those with rheumatoid arthritis, increased amounts of physical activity reduced circulating levels of CRP (30). The list of inflammatory-linked diseases that can be improved by regular activity is growing all the time.

However, not all studies have found a consistent decrease in inflammation (4, 39). Findings vary depending on the age of subjects, the length and intensity of exercise, how and when inflammation is measured, and the subject's starting fitness level. Despite the exceptions, most of the evidence points towards an anti-inflammatory effect of exercise and/or physical activity. For more details about the relationship of exercise and inflammation, several recent review articles are helpful (13, 24, 31, 43). Understanding how physical activity and exercise can most effectively lower inflammation both systemically and locally is key to making public health recommendations based on rigorous research.

However, in almost all of these examples, the reduction in inflammation is measured by systemic markers in the blood. Can the anti-inflammatory effects of exercise also been seen in local tissues? In one study that measured five inflammatory cytokines in wound tissue, exercised mice had lower levels of three cytokines, tumor necrosis factor alpha (TNF-α), monocyte chemotactic protein 1 (MCP-1), and keratinocyte chemoattractant (KC), and they also healed faster than sedentary controls (25).

EXERCISE AND OXIDATIVE DAMAGE

There is much evidence that the production of reactive oxygen species and resulting damage is increased in many populations, including the aged, diabetics, etc. (22, 23). In any person, damage caused by free radicals could result in delayed wound healing. Indeed, one consequence of prolonged hyperbaric oxygen therapy, designed to improve wound healing, is increased free radical production and potential tissue damage (2, 5, 35). However, there is strong evidence to suggest that moderate aerobic exercise can increase anti-oxidant enzyme activities which can

prevent damage caused by free radicals (18, 32).

Hoffman-Goetz et al. (21) reported an increase in expression of such enzymes (catalase and glutathione peroxidase) in mice after 16 weeks of freewheel running. Glutathione peroxidase and superoxide dismutase were increased in rats after one year of swim training (19). Similar results have been found in human subjects. In middle-aged obese women, six months of aerobic exercise (treadmill walking/running) resulted in higher resting levels of glutathione peroxidase and superoxide dismutase (37). Therefore, regular exercise may play a role in increasing the body's ability to prevent damage from free radicals, thus accelerating healing.

SUMMARY

For the millions of people around the world who suffer from impaired wound healing, finding effective, low-cost ways to improve healing is an urgent need. From a health care perspective, the increasing cost associated with chronic wounds also makes it a high priority. Since there are so many factors that can delay healing, including a sedentary lifestyle, the news that exercise may speed healing can be used by public health professionals to battle this growing problem. With the incidence of diseases associated with increased systemic inflammation on the rise, and since increased inflammation is known to delay healing, it is even more important to get the word out that exercise has the potential to decrease inflammation and damage from free radicals, allowing wounds to progress in a timely manner through the stages of healing. However, further research is needed to confirm the effects of exercise in other populations at risk, including the obese and diabetic, and to help elucidate the mechanisms responsible for this effect.

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