Psychological Stress and Wound Healing in Humans: What We Know

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Abstract: The phenomenon of stress is a common human experience frequently blamed for much of the ill health individuals experience. Much focus has been given to the effect of stress on health and wellness. Research demonstrates a strong relationship between psychological stress and health including, but not limited to, poor surgical outcomes and a decrease in immune system functioning. The skin is the largest organ of the human body and is responsible for thermoregulation, vitamin D production, and protection from fluid loss, pathogens, ultraviolet radiation, and mechanical injury. The skin contains a vast supply of sensory nerves, providing sensory input on pain, temperature, pressure, and pleasure. Timely wound healing is of utmost importance because of the skin’s vital protective and regulatory functions. Psychological stress has been shown to negatively impact wound healing, both directly and indirectly. The purpose of this review is to identify existing knowledge about the relationship between psychological stress and wound healing in order to provide the best evidence currently available on which to base recommendations for future research and to guide practice.

The phenomenon of stress is a common human experience frequently blamed for much of the ill health individuals experience. Much focus has been given to the effect of stress on health and wellness. Stress can be physical or psychological, acute or chronic. Stress is often thought of as the human response to a stimulus or more specifically a “stressor” in one’s environment. The response is often based on an individual’s appraisal of the situation, the individual’s coping behaviors, and the resources available to the individual. Lazarus and Folkman specifically define stress as a “relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her wellbeing.” Appraisal and coping are key to this definition and lead to the subjective experience of stress. The degree of perceived threat determines the magnitude of the stress response to the environmental event. When individuals can no longer cope with stressful situations, affective, behavioral, and
physiological changes result. Research demonstrates a strong relationship between psychological stress and health including, but not limited to, alteration in immune system functioning, poor surgical outcomes, alterations in metabolism, increased risk of obesity, and increased risk of developing cardiovascular disease.

The skin is the largest organ of the human body and is responsible for protection from pathogens, ultraviolet radiation, and mechanical injury. Additionally, the skin provides protection from fluid loss and has an active role in thermoregulation, as well as vitamin D production. The slightly acidic pH of the skin serves as a protective barrier against bacterial and fungal invasions. The skin contains a vast supply of sensory nerves that provide sensory input regarding pain, temperature, pressure, and pleasure.

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Wounds of the skin typically progress in a predictable and timely manner. When the normal phases of wound healing are interrupted, chronic wounds develop, which leads to an increased risk of infection, prolonged hospital stays, and decreased quality of life. Chronic wounds account for a significant amount of healthcare spending in the United States, amounting to an estimated $5 to $9 billion each year.

Stress has been shown to have a negative impact on wound healing. Although both the direct and indirect mechanisms of stress may be responsible for slowed healing, the most prominent impact is through the effects of stress on cellular immunity. Cellular immunity has an important role in the regulation of wound healing through the production and regulation of pro-inflammatory and anti-inflammatory cytokines. Cytokines, specifically platelet derived growth factor (PDGF), tumor necrosis factor (TNF-α), interferon-gamma (IFN-γ), various interleukins (IL-1α, IL-1β, IL-6, IL-8), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), and transforming growth factor beta (TGF-β) potentially mediate many of the complex interactions involved in wound healing.

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How Wounds Heal

A wound can be defined “a disruption of the integrity and function of tissues in the body” and can be further described according to its etiology (surgical, venous, neuropathic etc.), location (lower extremity, abdominal, foot, etc.) or by the duration (acute versus chronic). Normal cutaneous wound healing is a complex process that occurs in overlapping phases and depends upon interactions not only between the person and environment, but on multiple interactions among a large number of cells and chemical mediators including cytokines, hormones, and neurotransmitters. These phases do not occur in isolation, but are dynamic and overlapping. Even so, wound healing can be characterized by three phases: inflammatory, proliferative, and remodeling. The inflammatory phase begins within seconds of injury and lasts anywhere from 2–5 days. Blood vessel disruption activates platelets and triggers the release of clotting factors. The occurrence of vasoconstriction and platelet aggregation stops bleeding and provides a provisional matrix for cellular migration into the injured area. The large number of platelets in the clot will degranulate and release numerous growth factors and cytokines.

Approximately 24 hours after injury, neutrophils and macrophages begin to remove nonviable tissue, debris, and bacteria from the wound through the release of enzymes and phagocytosis. In addition to cleaning up the wound bed of nonviable tissue, macrophages and neutrophils have been shown to express several proinflammatory cytokines. Proinflammatory cytokines are some of the earliest signals to activate and recruit inflammatory cells and fibroblasts to the injury site causing inflammation and vasodilatation, which increases blood vessel permeability and allows easy passage of fluid and phagocytes. Platelet derived growth factor (PDGF) is released by the platelets, stimulating the growth of blood vessels and new structural tissue. Cytokines are also responsible for activation of keratinocytes found at wound edges, hair follicles, sebaceous and sweat glands. Keratinocytes are the most prevalent cell type of epithelium and begin to migrate and proliferate within 24 hours after injury, paving the way for the formation of new epithelium. This process continues on into the proliferative phase of wound healing.

Over the next 2 to 3 weeks, the proliferative phase begins. Fibroblasts and other cell types begin to lay down the ground substances and collagen fibers in the site of injury. Various chemical mediators such as PDGF stimulate angiogenesis, which is marked by the formation of granulation tissue consisting of new capillary loops in a matrix of collagen and ground substance. Keratinocytes are actively carrying out re-epithelializa-
tion. Wound contraction is accomplished by the work of the myofibroblasts. The wound is considered closed with the establishment of a new epidermal covering. The basement membrane, between the epidermis and the dermis, is typically repaired 7–9 days after re-epithelialization and is essential for the restoration of skin integrity and function.29

Over the next 3 weeks to 2 years, the final phase of wound healing takes place. In the maturation or remodeling phase, type III collagen is gradually replaced with type I. Tensile strength increases as the collagen fibers reorganize. Healed wounds result in a scar, which differs somewhat from the original tissue, and has approximately 70%–80% of its original tensile strength.25

**KEYPOINTS**

- For inclusion in this review, all studies had to have at least one measure of stress, such as the Perceived Stress Scale (PSS). Studies exploring the relationship between other psychological factors, such as depression or anxiety, were not included in this review.

## The Stress Response

Often when we think of the stress response, we think of the “Fight or Flight” response, whereby stressful events trigger simultaneous activation of both the hypothalamic-pituitary-adrenal (HPA) axis in the central nervous system and the sympathetic-adrenomedullary (SAM) axis in the sympathetic nervous system. Activation of the SAM axis stimulates the release of the catecholamines epinephrine and norepinephrine, leading to an increased heart rate, increased blood flow to skeletal muscles, and an elevation in glucose metabolism. The SAM pathway is faster and has a more immediate physiological effect. Activation of the SAM axis activates the inflammatory response.

Activation of the HPA axis activates the release of corticotropin-releasing hormone (CRH) from the hypothalamus and CRH then stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn triggers the release of the glucocorticoids from the adrenal glands. In humans, this glucocorticoid is cortisol. Normal levels of glucocorticoids are believed to be immunomodulatory. However, when stress increases levels of glucocorticoids, suppression of inflammatory and immune responses occurs.30 Cortisol has been shown to decrease circulating leukocytes and inhibit the migration of leukocytes to the site of injury or infection by decreasing capillary permeability and inhibiting chemotaxis. Elevated cortisol levels have been found to inhibit production of T cell-derived cytokines, such as interleukin 1.

## Stress and Wound Healing

It is well established that psychological stress modulates immune system functioning and a fully functioning immune system is integral to timely and effective wound healing. Numerous studies have explored the relationship between psychological stress and wound healing. Although both human and murine models have been utilized in studying stress and wound healing, only studies involving human subjects will be included here. For inclusion in this review, all studies had to have at least one measure of stress, such as the Perceived Stress Scale (PSS). Studies exploring the relationship between other psychological factors, such as depression or anxiety, were not included in this review.

Systemic factors known to have negative effect on wound healing were considered exclusion criteria and were similar across all studies. Exclusion criteria most commonly cited included tobacco use, diabetes, peripheral vascular disease (PVD), cardiovascular disease (CVD), difficulty with wound healing in the past, immunologically related problems, recent surgeries, previous psychiatric illnesses, and use of anti-inflammatory medications with obvious immunological effects. Smokers and individuals with frequent alcohol consumption were often excluded. Wound types consisted of experimentally created wounds (eg, punch biopsy, blister) or preexisting clinical wounds (surgical and leg ulcers). Research utilized a variety of measures to evaluate the relationship between psychological stresses and wound healing. This makes a comparison of studies somewhat difficult since outcome measures varied. For the purpose of this review, findings are grouped based on how healing was assessed.
Digital Photography

The most simple and straightforward method of wound assessment is the use of digital photography. In a study of the effectiveness of a 3-month exercise intervention program on wound healing, neuroendocrine function, and perceived life stress, Emery et al. utilized digital photography to assess wound healing. The wound healing outcome measure was the ratio between the areas of a standardized black dot applied next to the wound. Photos were taken on a schedule and wound healing was documented and considered positive as the size of the wound decreased in relation to the applied dot. A sample of 28 healthy men and women were randomized to either an exercise intervention group or a control group. The wounds of individuals who participated in regular exercise healed significantly faster (mean = 29.2, SE 9.0 days). All wounds for both groups healed by week 7. Interestingly, this study found that exercise improved healing yet did very little to improve self-reported stress on the PSS. Salivary cortisol was elevated in the exercise group but did not change in the nonexercise group. The authors proposed that the increased responsiveness of cortisol to stress following exercise suggests that exercise contributes to enhanced neuroendocrine responsiveness.

High Resolution Ultrasound

Ultrasounds use sound waves to produce images of soft tissue anatomy. Basically, a probe is placed over the area of interest and transmits sound waves into the body. When these sound waves hit a boundary between acoustically different tissues, such as bone versus soft tissue, a proportion of the energy, known as an echo, is reflected back. High-resolution ultrasound typically involves frequencies of 15 megahertz (MHz) or higher. Depth of penetration is lost with higher frequencies, but resolution is improved. High-resolution ultrasound is useful in that it can show the fluid content of various tissues. Greater fluid content results in a decrease in the echogenicity in the tissue being observed. The use of high-resolution ultrasound has been shown to be effective in assessing dermal wounds.

Ebrecht et al. utilized high-resolution ultrasound in evaluating the healing of wounds placed on the hard palate. A prospective, longitudinal design with random assignment was used to test the ability of a disclosure intervention to lower psychological stress associated with a traumatic experience and to improve healing. While the disclosure intervention did not have a significant effect on the PSS scores, participants who wrote about emotional experiences had significantly faster wound healing times (wounds ~11% smaller) than the control group.

Hydrogen Peroxide Foaming Test

Two studies identified for this review utilized the hydrogen peroxide response test to assess wound healing. This method measures the quality of the epithelial barrier. The process involves the application of a small amount of hydrogen peroxide to the wounded area. Catalase, an enzyme found in connective tissue, liberates oxygen gas and water from the hydrogen peroxide. If the epithelial layer is disrupted, then foaming is visible at the wound site as oxygen is liberated. If the epithelial layer is intact, the diffusion of hydrogen peroxide does not take place and therefore little or no foaming is visible. Therefore, if there is no foaming present after application, the wound is considered healed.

Marucha et al. evaluated the effects of examination stress on dental students' ability to heal a mucosal wound. Each subject served as his or her own control. Two wounds were placed on the hard palate, the first during summer vacation. The second wound was placed on the contralateral side 3 days before the first major examination of the term. Daily photographs and foaming response to hydrogen peroxide were used to measure healing. Students took significantly longer to heal during the examination period (mean 7.82 days) compared to the vacation period (mean 10.91 days) [F(1,10) = 28.47; *P* < 0.001] Students scored higher on the PSS and had lower whole blood IL-1β levels during examinations. The decrease in IL-1β demonstrates the decrease in immune function and a possible mechanism underlying the relationship of examination stress to wound healing.

Kiecolt-Glaser et al. used hydrogen peroxide foam...
test to evaluate the effects of psychological stress caused by caring for a relative with Alzheimer’s disease on wound healing. Healthy female caregivers and controls were studied simultaneously, matched for age and income. Complete wound healing of a 3.5-mm punch biopsy, as indicated by lack of foaming after the application of hydrogen peroxide, took significantly longer in caregivers (mean 48.7 days, SE = 2.9) than controls (mean 39.3 days, SE = 3.0). Wound healing took on average 9 days longer in caregivers than in controls. In addition, caregivers reported significantly more stress on the PSS than did control participants on study entry (20.5, SE = 1.6 versus 13.7, SE = 1.5, P < 0.002). There was no significant change during the study, nor was there an interaction between group and time.

### Wound Fluid Analysis

Since numerous chemical mediators and cell types are involved in the complex process of wound healing, analysis of wound fluid provides some insight into the extracellular environment of the wound. \(^1\) \(^2\) \(^3\) \(^4\) \(^5\) Wound fluid characterization provides the opportunity to obtain information reflecting the status of the wound at specific time points, and holds potential for the development of specific biomarkers of impaired healing. \(^6\) Analysis of wound fluid provides an opportunity to potentially connect the mechanisms of psychological stress to cellular mechanisms in the local wound site.

In one prospective, longitudinal, observational study, Glaser et al. \(^7\) \(^8\) \(^9\) \(^10\) \(^11\) \(^12\) assessed the relationship between perceived life stress and the production of pro-inflammatory cytokines at the wound site. Blister wounds were created on 36 healthy female subjects and wound fluid was analyzed. Psychological tests included the 10-item Perceived Stress Scale (PSS), the Positive and Negative Affect Schedule, and the Psychiatric Epidemiological Research Inventory Life Events Scale. Health-related behaviors were also assessed. Women reporting greater stress had lower production of IL-1α [F(1,32) = 5.73, P < 0.03] and IL-8 [F(1,32) = 5.31, P < 0.03] in the wound blister fluid.

In a second prospective longitudinal study, Broadbent et al. \(^13\) evaluated the relationship between preoperative stress and worry and wound healing in patients undergoing routine surgical repair for an inguinal hernia. Psychological measures included the PSS, the Worry Visual Analogue Scale, and the Mental Health Index. Wound healing was determined through changes in cytokine profiles of surgical wound fluid collected from the routine manovac drain placed at the time of surgery. Higher reported preoperative psychological stress predicted impaired cellular wound repair processes in the early postoperative period. For example, higher preoperative stress significantly predicted lower levels of IL-1 in the wound fluid (β = -0.44; P = 0.03). Greater worry about the surgery predicted lower levels of matrix metalloproteinase-9 in the wound fluid (β = -0.38; P = 0.03), a more painful recovery (β = 0.51; P = 0.002), and slower recovery (β = 0.43; P = 0.01). Neither stress nor worry predicted lower levels of IL-6 levels in the wound fluid. Interestingly, researchers did not exclude smokers. Smokers had higher levels of peripheral blood MMP-9 concentrations. Prolonged MMP-9 elevation has been associated with chronic non-healing wounds. \(^14\) Lower cytokines were also associated with higher cortisol levels.

Lastly, Keicoll-Glaser et al. \(^15\) \(^16\) \(^17\) explored the effect of hostile marital relationships on wound healing. A group of 42 healthy married couples, aged 22 to 77 years (mean 37.04) who were married a mean of 12.55 years, were enrolled in an experimental cross-over study. Couples were engaged in a structured social support interaction during the first phase of the study, and in the second phase, were asked to discuss a marital disagreement. Psychological evaluations included the Positive and Negative Affect Schedule (PANAS) and the Marital Adjustment Test, which provided data on marital satisfaction (higher scores indicate higher satisfaction). The Rapid Marital Coding System provided data on behavior during both phases of the study. Wound fluid was evaluated for changes in cytokine levels. In addition, wound healing was measured by the rate of transepidermal water loss (TEWL) using an evaporimeter, which is a non-invasive objective method to evaluate changes in the stratum corneum barrier function of the skin. \(^18\) They found that couples’ blister wounds healed more slowly following a single 30-minute marital conflict discussion.

### Keypoints

- This review provides but a glimpse of what is known and what is still left to be discovered in the exciting area of psychological stress and wound healing. Other psychological mediators, such as depression and anxiety, have been shown to slow wound healing and should be explored further.
- Future work to examine the exact mechanisms of pro-inflammatory and anti-inflammatory cytokines will shed additional light on the mechanisms of stress on wound healing.
in a controlled setting in comparison to healing rates following supportive interactions \( (P = 0.01) \). Wound fluid cytokines (ie, IL-6, TNF-\( \alpha \), and IL-1\( \beta \)) were also lower after conflict in comparison to social support. Additionally, participants with high-hostility behavior healed more slowly than the low-hostility behavior group \( (P = 0.03) \).

Conclusion

Clearly, there are substantial data in human studies to suggest that psychological stress and the subsequent effect on immune system disruption can impact wound healing. The purpose of this article is to serve as a foundation and a review of the existing literature on the relationship of psychological stress and wound healing in humans. Additionally, a review of available tools to measure wound healing for nursing research was presented. This article provides but a glimpse of what is known and what is still left to be discovered in the exciting area of psychological stress and wound healing. Other psychological mediators, such as depression and anxiety, have been shown to slow wound healing\(^{47-49} \) and should be explored further. Psychological stress can lead to unhealthy behaviors which may impact wound healing such as smoking,\(^{50} \) poor nutrition,\(^{51} \) and altered sleep.\(^{52} \) For example, Rose et al\(^{52} \) point out that stress can negatively impact sleep, leading to disturbed sleep patterns and a reduction in growth hormones, which may down-regulate the tissue repair response.

Although numerous factors play a role in whether or not a wound heals, such as nutrition, underlying health conditions and appropriate care, it is clear that cytokines play a crucial role as well. If dysregulation of the various cytokines occurs, a potential disruption of normal wound healing results, leading to delayed healing and increased risk of infection and wound complications. Future work to examine the exact mechanisms of pro-inflammatory and anti-inflammatory cytokines will shed additional light on the mechanisms of stress on wound healing. Examination of wound fluid holds the potential to identify biomarkers of wound healing and subsequently provide diagnostic information on the wound environment to improve treatment modalities.

References


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