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REVIEW

The Impact of Psychological Stress on Wound Healing: Implications for Neocollagenesis and Scar Treatment Efficacy

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Abstract: Psychological stress is a well-established inhibitor of wound healing, yet its specific impact on scar treatment efficacy remains underexplored. Given the significance of collagen synthesis in wound healing and various advanced scar treatments, an investigation into the impact of psychological stress on these processes is warranted. This review examines the biological mechanisms of wound healing and collagen formation, focusing on how psychological stress disrupts these pathways and impacts scar treatment outcomes. Current literature indicates that psychological stress impairs collagen production and reduces the efficacy of scar treatments. These findings underscore the importance of integrating stress management into scar treatment protocols and highlight the need for further research into combined physiological and psychological approaches to optimize healing.

Keywords: collagen, fibroblasts, sympathetic nervous system, hypothalamic-pituitary-adrenal axis, immune system

Introduction

Wound healing is essential for restoring skin integrity, with collagen playing a central role in tissue repair and scar formation.[1] When collagen synthesis or remodeling is disrupted, it can lead to complications such as dermal thinning, poor cosmetic outcomes, and weakened skin structure.[2] Since many scar treatments aim to stimulate collagen production to enhance scar appearance or rely on effective wound healing to achieve the desired result, factors that disrupt collagen formation pose significant risks to aesthetic outcomes and effective healing.[3]

One factor known to disrupt wound healing is psychological stress, defined as emotional strain caused by perceived challenges or threats.[4] A state of emotional strain and pressure that stems from an individual perceiving a situation as challenging or threatening.[4] Psychological stress and mental health concerns are increasingly common in today's fast-paced, high-pressure environment, yet their effects on physical healing are often underestimated.[4] While stress is a normal human response to everyday pressures, it can become unhealthy, manifesting in harmful effects for both mental and physical health.[5] As a result, psychological stress plays a crucial yet often underestimated role in wound healing, influencing various physiological pathways.[6]

Studies have shown that psychological stress can interfere with all phases of wound healing, hemostasis, inflammation, proliferation, and remodeling, by disrupting cytokine signaling, immune cell function, and fibroblast activity.[3,7] These disruptions can compromise collagen synthesis and extracellular matrix remodeling, resulting in less organized and structurally weaker tissue.[7] This interference is driven by stress-induced activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis (HPA axis), which cause complications such as prolonged exposure to catecholamines and glucocorticoids (GCs).[6,8] Stress-related factors also disrupt immune regulation, impair fibroblast function, and disturb cytokine balance, further hindering collagen production and tissue repair.[9,10] While the general health impacts of stress are well established, its specific role in impairing wound healing and collagen synthesis requires more focused investigation.

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Since stress can impair collagen production and delay healing, incorporating stress management strategies, such as mental health support, into scar treatment protocols may help improve patient outcomes. This highlights the need for scar treatment strategies that not only target the biological aspects of healing but also address psychological factors that can interfere with tissue repair. By integrating stress reduction and mental health interventions into treatment plans, clinicians may enhance both the physical and emotional recovery process.[11] Effective scar treatments are essential not only for improving appearance, but for restoring skin function and preventing complications like pain, limited mobility, and the psychological burden that some scars carry.[12] Addressing these challenges opens important opportunities for both clinical practice and research, with the potential to improve treatment outcomes and enhance patients' overall well-being.[12] This review examines the complex interplay between psychological stress and scar healing, with a focus on the biological pathways that influence collagen production and remodeling, emphasizing the need for a more holistic, patient-centered approach to care.

Materials and Methods

A comprehensive search of PubMed and PubMed Central was conducted to identify papers related to psychological stress, wound healing, collagen synthesis, and scar treatments. The primary search terms included psychological stress, wound healing, collagen synthesis, and scar treatments. A second search round was performed to address key physiological mechanisms, clarify inconsistencies in existing research, and expand the discussion of how psychological and physiological factors interact in scar healing. Two additional articles were identified directly from journal websites that were not indexed in the databases.

In total, 1557 records were retrieved (744 from PubMed, 813 from PMC). After deduplication using Zotero, 1,070 unique records remained. Screening was performed in Rayyan by three independent reviewers, using predefined inclusion and exclusion criteria. Studies were included if they were peer-reviewed, in English, and examined biological, mechanistic, or clinical links between psychological stress, skin wound healing, collagen synthesis, or scar treatment outcomes. Studies were excluded if they were non-English, focused on non-skin tissues, or lacked relevant stress or healing outcomes. After full-text review, 96 studies were included in the final synthesis. The selection process is summarized in the PRISMA flow diagram outlined in Figure 1.[13]

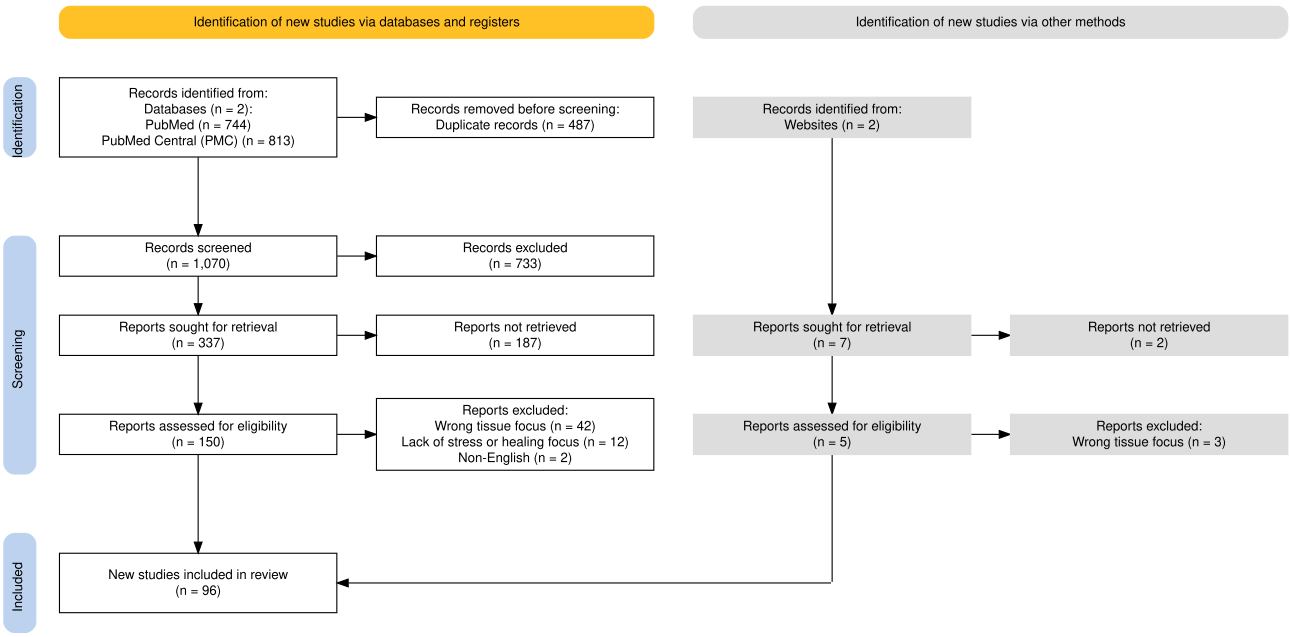

Figure 1 PRISMA flow diagram showing study selection from 1,557 identified records on PubMed and PubMed Central to 96 studies included in the final review paper.
Notes: PRISMA figure adapted from Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA 2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. Campbell Syst Rev. 2022;18:e1230.[13]

Biological Mechanisms of Wound Healing

Wound healing advances in four overlapping but distinct biological phases: hemostasis, inflammation, proliferation, and remodeling, as shown in Figure 2.[3] Disruptions at any stage cane impair the wound-healing process and result in poor cosmesis.[7]

Hemostasis is initiated immediately after injury, with platelet aggregation and clot formation to prevent excessive bleeding and provide a scaffold for healing.[14] The inflammatory phase follows, marked by increased vascular permeability and recruitment of immune cells.[15] These cells, guided by cytokines and growth factors, help protect against infection and regulate the fibroblast and epithelial cell functions critical for tissue repair.[15] Inflammatory cytokines trigger a cascade of cellular responses, promoting collagen production and activating matrix metalloproteinases (MMPs), which degrade damaged extracellular matrix (ECM) components to support tissue remodeling.[16]

The proliferative phase involves the activation of fibroblasts, leading to the formation of granulation tissue.[17] Fibroblasts initially produce type III collagen and other ECM components, while myofibroblasts contribute to wound contraction.[18,19] Neocollagenesis, the process of forming new collagen, begins shortly after injury and continues for several weeks, reinforcing tissue integrity.[19] The final phase, remodeling, involves the reorganization of the ECM and collagen maturation.[20] Type III collagen is gradually replaced by stronger type I collagen, a process regulated by MMP activity.[20]

Understanding the molecular players in each of these phases of wound healing helps identify how disruptions, such as altered cytokine signaling or impaired fibroblast function, can interfere with collagen production and ECM remodeling.[21] Any disruptions during these phases, such as those occurring during prolonged stress, can result in less effective healing and poor scarring.[21]

Collagen and Wound Healing

Collagen types I and III, triple-helix proteins, are the main structural proteins involved in skin wound healing.[1] Type III collagen is a thinner and more flexible form found in the papillary dermis. This collagen plays a key role in early wound healing, forming a provisional ECM that supports angiogenesis and fibroblast migration.[1,8] As healing progresses, type III collagen is replaced by type I collagen, which provides greater tensile strength and structural support in the reticular dermis and scar tissue.[22]

The synthesis of collagen during wound healing is tightly regulated by several key signaling pathways, as summarized in Figure 2, most notably the transforming growth factor-beta (TGF-β) pathway, which promotes fibroblast activation and collagen production, but can also lead to fibrosis if overactivated.[2,23] Collagen synthesis is regulated by several key signaling pathways. The transforming growth factor-beta (TGF-β) pathway promotes fibroblast activation

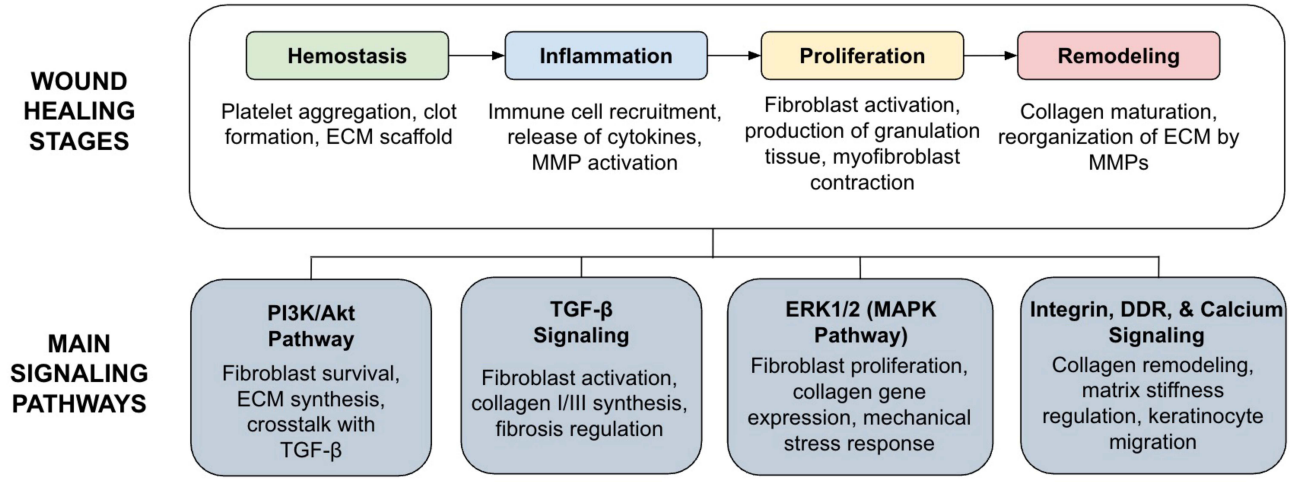

Figure 2 Stages of Wound Healing and Key Signaling Pathways. This diagram outlines the key wound healing stages and their associated cellular signaling pathways regulating repair and remodeling.

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and collagen production but can cause fibrosis if overactivated.[2,23] The PI3K/Akt pathway further supports collagen synthesis by promoting fibroblast survival and ECM production, often working alongside TGF-β.[24] Similarly, the ERK1/2 branch of the mitogen-activated protein kinase pathway regulates fibroblast proliferation and collagen gene expression in response to mechanical stress, cytokines, and growth factors.[24] Integrin and discoidin domain receptor pathways contribute to collagen remodeling and cell migration, while calcium signaling facilitates keratinocyte movement during early healing.[2,25] Crosstalk between these pathways ensures a tightly regulated balance between collagen synthesis and degradation.[25]

Proper coordination of collagen synthesis, remodeling, and degradation is essential for effective wound healing and scar quality. Factors such as genetics, age, and fibroblast activity influence this balance and affect scar outcomes.[26] Hypertrophic scars develop from excessive fibroblast activity and collagen deposition, often due to an imbalance between type I and III collagen synthesis and degradation.[26,27] In contrast, atrophic scars form when fibroblast activity is reduced, collagen production is insufficient, or collagen is broken down too quickly, leading to tissue loss and skin depressions.[28] Maintaining the balance between type I and III collagen, along with the carefully regulated collagen synthesis and degradation, is vital for effective wound healing.[2] The following sections will explore how psychological stress disrupts these processes and its implications for scarring outcomes and treatment efficacy.

Mechanistic Contributors to Collagen Synthesis and Remodeling

The Sympathetic Nervous System

The sympathetic nervous system (SNS) is activated in response to stress, influencing immune function and skin health.[29] Catecholamines like epinephrine and norepinephrine (NE) are released during SNS activation, increasing heart rate, blood pressure, and energy mobilization.[30] While these responses are adaptive in the short term, chronic SNS activation maintains the body in a state of readiness rather than repair, impairing tissue regeneration and immune regulation, as summarized in Figure 3.[9,31]

In the skin, norepinephrine (NE) binds to β2-adrenergic receptors (β2ARs), influencing blood flow, inflammation, and barrier function.[32] During stress, elevated NE levels amplify these effects, which can interfere with normal skin healing. Stress-induced overactivation of β2ARs during stress can worsen inflammation, slow keratinocyte migration, and delay re-epithelialization, processes critical for wound healing.[3,33] This was demonstrated in a mouse study by Denda et al, where applying a topical β2AR agonist delayed skin barrier repair, while a β2AR antagonist accelerated barrier

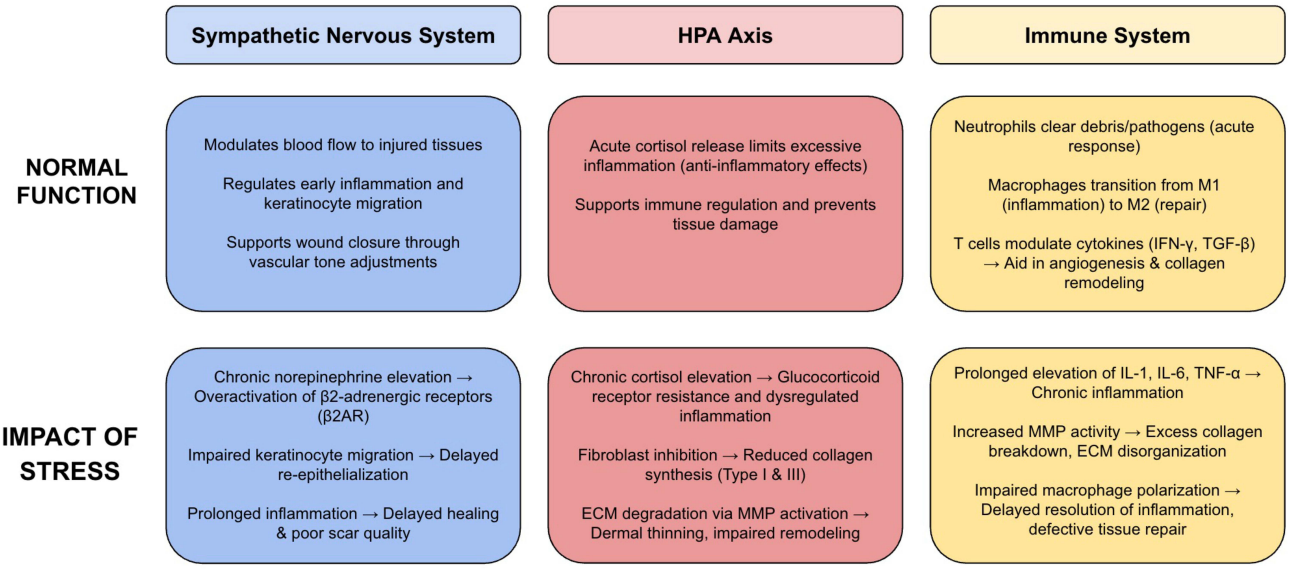

Figure 3 Mechanistic Contributors to Collagen Synthesis and Remodeling. This diagram compares the normal roles of the sympathetic nervous system, HPA axis, and immune system in wound healing with the detrimental effects of chronic stress.

recovery.[9,33] Additional studies found that NE depleted mice had a weaker initial inflammatory response but higher levels of angiogenesis and have shown improved collagen arrangement.[9] These findings illustrate how SNS overactivation during stress can disrupt normal wound healing.

The Endocrine System

Alongside the SNS, the endocrine system, particularly the HPA axis, plays a key role in the stress response by regulating GC release, primarily cortisol.[8] This process involves a signaling cascade: the hypothalamus releases corticotropin-releasing hormone, which stimulates adrenocorticotropic hormone production in the pituitary gland, leading to cortisol release from the adrenal cortex.[34] The HPA axis is tightly regulated by negative feedback mechanisms, where GCs bind to GRs to suppress further hormone release and maintain homeostasis.[35]

In response to an acute stressor, this system is beneficial, providing protective and adaptive benefits, as displayed in Figure 3. GCs help to modulate inflammation by limiting immune overactivation, promoting anti-inflammatory macrophage activity, and reducing excessive cytokine release.[36] However, chronic stress can disrupt the HPA axis feedback sensitivity, leading to GC dysregulation and prolonged exposure to inflammatory mediators.[37] FK506-Binding Protein 5 (FKBP5), a co-chaperone protein, is a key regulator in this process.[36,38] When overexpressed, FKBP5 reduces GR sensitivity, limiting the body's ability to resolve inflammation and prolonging the stress response.[36,38]

While short-term GC release is essential for immune regulation, prolonged exposure harms skin integrity and overall wound healing.[8] Chronic GC elevation is associated with dermal thinning, impaired healing, and accelerated skin aging.[8,39] These effects result from decreased fibroblast activity, increased MMP-2 activity, and GC-induced GR resistance.[40] The dermis, in particular, suffers from reduced fibroblast function and compromised collagen synthesis, leading to structural skin weakening, and thinning of the dermis is primarily associated with reduced collagen levels and accelerated aging.[35] One human fibroblast study found that topical GC application reduced type I and type III collagen mRNA levels by 70%, with an overall 80% decrease in collagen production.[41] This demonstrates how GCs directly impact dermal integrity and tissue structure by suppressing collagen synthesis.

The Immune System

The immune system is closely coordinated with the HPA axis, and as chronic stress disrupts GC regulation, immune signaling is also affected, as displayed in Figure 3.[42] Several immune mediators are involved in regulating inflammation, tissue repair, and fibroblast activity.[42] These include interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interferon-beta (IFN-β), interferon-gamma (IFN-γ), MMPs, chemokines, cytokine receptors, and various T cell subsets.[9,10,43,44]

During acute stress, cytokines like IL-1 and TNF-α increase temporarily, supporting immune surveillance and triggering a controlled inflammatory response.[45] IL-1 stimulates fibroblast proliferation and upregulates MMP-2, maintaining a balance between collagen synthesis and degradation.[35,46] IL-1 promotes fibroblast proliferation and activates MMP-2, helping to balance collagen production and degradation.[35,46] Similarly, TNF-α also plays a role by recruiting macrophages and supporting the early stages of wound healing.[24] However, with chronic stress and ongoing GC exposure, this balance is disrupted. Persistently high IL-1 levels lead to overstimulation of MMP-2, leading to excessive collagen breakdown and weakening the dermal matrix.[47,48] Elevated TNF-α further impairs healing by reducing fibroblast-driven collagen production, compromising tissue integrity.[24] Additionally, increased FKBP5 expression reduces GR sensitivity, limiting the body's ability to resolve inflammation and prolonging tissue damage.[49]

IL-6 has a multi-faceted role in healing: it promotes leukocyte activation, supports endothelial and keratinocyte activity, and aids fibroblast differentiation.[50] IL-6 is key in transitioning the wound from an inflammatory state to a reparative one.[50] However, elevated IL-6 levels from stress hormones can also sustain inflammation and promote excessive fibroblast proliferation, contributing to keloid formation, as one study found.[10] Moreover, patients with keloids often experience ongoing psychological stress related to cosmetic concerns, discomfort, or trauma, which perpetuates this cycle of inflammation and fibrosis.[10] This illustrates how chronic stress can disrupt normal wound healing, leading to excessive fibrosis and impaired tissue repair.

Interferons also regulate immune responses during wound healing. IFN-β suppresses excessive immune activation and modulates fibroblast proliferation.[51,52] However, chronic GC exposure can lower IFN-β levels, exacerbating inflammation and hindering wound resolution.[51,52] IFN-γ, while beneficial in early wound healing by activating macrophages, becomes harmful when chronically elevated.[53] Chronic stress increases IFN-γ levels, impairing fibroblast function and disrupting collagen remodeling.[54]

Furthermore, chemokines such as CCL2, CXCL8, and CXCL12 help recruit immune cells and direct fibroblast migration to the wound site.[43] These molecules guide neutrophils, macrophages, and other immune cells to ensure a coordinated inflammatory response.[43] T lymphocytes, especially CD4+ helper T cells, modulate immune responses and support tissue regeneration.[44] Regulatory T cells (Tregs) help control inflammation and promote the resolution of wound healing.[44] Overall, these interactions show how immune dysregulation under chronic stress can significantly impair wound healing.

Ultimately, the interplay between sympathetic nervous activation, endocrine regulation, and immune signaling determines the wound healing trajectory. As summarized in Figure 3, while the acute responses are protective and adaptive, chronic stress disrupts their balance, impairing fibroblast function, collagen synthesis, and overall tissue repair.

Other Contributors to Collagen Synthesis and Remodeling

Several environmental and lifestyle factors significantly influence collagen synthesis and remodeling during wound healing. Among these, dietary habits, UV exposure, topicals, and smoking are well-established contributors.[55–57]

Dietary habits, particularly diets high in sugar, promote the formation of advanced glycation end-products, which interfere with normal collagen structure. AGEs create abnormal cross-links, increase oxidative stress, and activate MMPs, leading to collagen degradation.[55] Together, these effects weaken the dermal matrix and impair the skin's ability to repair itself.[55] Chronic ultraviolet exposure has similar effects, accelerating collagen breakdown by generating reactive oxygen species and increasing MMP activity, contributing to photoaging and compromised wound healing.[55]

Conversely, ascorbic acid is essential for collagen synthesis, serving as a cofactor for hydroxylases that stabilize the collagen triple helix.[56] A deficiency in ascorbic acid impairs collagen formation and delays wound healing.[56,57] Retinoids, commonly used to enhance epidermal turnover, also have complex effects on collagen synthesis.[58] Some studies suggest that at high concentrations, retinoids may inhibit collagen production in fibroblasts, while in other contexts they can support extracellular matrix remodeling and improve dermal structure.[58] Proteoglycans like decorin and biglycan are also important for neocollagenesis and fiber organization.[59] By binding to collagen and modulating TGF-β signaling, they influence scar formation and determine tissue tensile strength.[59]

Another important contributor, smoking, disrupts collagen production through several mechanisms, including vasoconstriction, reduced oxygen supply, and increased oxidative stress. These effects collectively delay wound healing and worsen scar quality.[60] These examples highlight how external factors can modulate collagen synthesis and remodeling, directly affecting wound healing outcomes and overall tissue integrity. Recognizing these influences is essential for understanding collagen dynamics in wound healing and identifying modifiable factors that could enhance tissue repair. The following sections will explore how these mechanisms impact scar treatment efficacy and examine strategies to mitigate stress-related barriers to optimal skin regeneration.

The Impact of Psychological Stress on Scar Treatments

As established, wound healing is a complex, multi-system process, and chronic psychological stress can disrupt key functions like collagen synthesis.[21] Because many scar treatments rely on stimulating collagen production for optimal results, stress-induced disruptions can significantly reduce their effectiveness.[61] This section examines how stress impacts scar treatments that either stimulate neocollagenesis or depend on efficient wound healing, underscoring the importance of stress management in scar treatments.

Collagen-Stimulating Treatments: Promoting New Tissue Formation

Scar treatments that directly stimulate collagen production can enhance skin texture and reduce scar visibility.[61] By promoting collagen synthesis, these treatments aim to restore volume, improve fiber alignment, and enhance thickness and elasticity.[62]

Subcutaneous Incisionless Surgery

Subcutaneous incisionless surgery (subcision) is a minimally invasive technique used to treat atrophic scars.[62] Subcision involves inserting a needle beneath the scar to break through fibrous bands, releasing tethered skin and allowing the tissue to reposition.[62] This mechanical disruption triggers a localized hematoma, which in turn stimulates fibrosis and promotes new collagen formation.[63] Subcision is often combined with dermal injections like poly-l-lactic acid to further enhance collagen synthesis and restore volume.[62] Successful healing after subcision depends on a coordinated inflammatory response and active fibroblast function, both of which can be impaired by stress-related physiological changes.[3,64] Chronic stress elevates GC levels, which impair fibroblast proliferation and reduce collagen synthesis. This undermines the structural support needed for effective scar remodeling.[65] Stress-related disruptions in inflammatory signaling can also impair hematoma formation and subsequent fibrosis, both critical for achieving the lifting effect of subcision.[10,62] Because subcision relies on effective neocollagenesis and tissue remodeling, stress-induced impairments in these processes can ultimately reduce its effectiveness. This demonstrates the importance of managing psychological stress as part of optimizing treatment outcomes, reinforcing the need for a more integrative approach to scar care.

Chemical Approaches

Chemical treatments like chemical peels and the chemical reconstruction of skin scars (CROSS) technique promote skin remodeling by creating controlled epidermal injury, which stimulates collagen production.[66] Chemical peels involve applying acid solutions, such as trichloroacetic acid (TCA) or phenol, to exfoliate superficial skin layers.[67] This controlled injury triggers epidermal regeneration and improves overall skin texture.[67] The CROSS technique is commonly used for atrophic scars like icepick scars, and the targeted application of a high-concentration acid directly onto the scar tissue to stimulate localized remodeling.[66] In addition to impairment of fibroblast activity, stress-related alterations in inflammatory signaling may prolong the wound-healing phase, affecting the deposition of new collagen and delaying epidermal regeneration.[68] As a result, patients under significant psychological stress may experience slower healing and see less improvement in scar texture after CROSS or chemical peel procedures. Because these treatments depend on robust collagen formation, stress-induced molecular disruptions can interfere with their intended effects; individuals experiencing high stress may have reduced collagen deposition, limiting the effectiveness of these treatments. Incorporating stress management into scar treatment plans could be key to improving outcomes with collagen-stimulating procedures.

Collagen-Dependent Treatments: Enhancing Outcomes Through Optimal Collagen

Other scar treatments, such as dermabrasion, surgical revision, and resurfacing lasers, do not directly stimulate collagen production, but rely on the body's ability to heal properly at each stage of the wound healing process to achieve optimal results.[69] Although collagen stimulation is not the primary mechanism of these treatments, any disruption in wound healing can compromise their success, as they depend on effective tissue repair and healthy skin structures.[69] Chronic psychological stress can delay healing, impair tissue regeneration, and prolong inflammation, factors that can reduce the effectiveness of these treatments.[68]

Dermabrasion

Dermabrasion is a mechanical resurfacing procedure that removes the skin's outer layers to smooth texture and create a more even appearance.[70] The controlled injury caused by dermabrasion stimulates new epithelial growth and promotes collagen remodeling in deeper skin layers.[70] However, successful outcomes depend on the skin's capacity for effective regeneration. Psychological stress can hinder healing after dermabrasion by elevating pro-inflammatory cytokines and GC levels, which slow down epithelialization and collagen deposition.[71] Stress-induced vasoconstriction also limits oxygen and nutrient delivery to the treated area, further impairing healing and increasing the risk of poor outcomes.[3,7] Because dermabrasion depends on effective wound healing, stress-related physiological disruptions can limit its benefits. Incorporating stress management strategies may help improve recovery and enhance treatment outcomes.

Surgical Scar Revision

Surgical scar revision involves excising or repositioning scar tissue to improve both appearance and function.[72] Techniques like Z-plasty, W-plasty, or punch excision are chosen based on the scar's characteristics and location, aiming to realign tension lines and reduce visibility.[72] Although these procedures rely on surgical precision rather than directly stimulating collagen, their success depends on proper wound healing, a process that chronic stress can significantly disrupt.[3,7] Stress-induced increases in MMP-2 activity can degrade newly formed collagen, weakening the structural integrity of the revised scar.[16,48] Furthermore, stress-driven dysregulation of IL-1 and TNF-α can prolong inflammation, delay wound closure, and raise the risk of hypertrophic or widened scars.[68] A study on keloid recurrence after surgical removal further illustrates stress's impact: patients with higher stress responses, measured by galvanic skin response, had an increased risk of keloid recurrence.[73] Since surgical scar revision aims to improve both appearance and function, stress-related disruptions to healing can not only compromise cosmetic results but also increase the risk of recurrence or excessive scarring.[3,68] These findings highlight the importance of incorporating stress management into post-surgical care to support better healing and long-term outcomes.

Resurfacing Lasers

Energy-based treatments like carbon dioxide (CO2) lasers and erbium yttrium-aluminum-garnet (Er:YAG) lasers are commonly used in scar management, especially for resurfacing and improving the texture of scarred.[74] CO2 lasers use concentrated thermal energy to vaporize damaged skin layers, promoting dermal collagen remodeling.[75] In contrast, Er:YAG lasers precisely ablate superficial layers to stimulate controlled wound healing and new tissue generation.[76] Psychological stress can impair extracellular matrix (ECM) formation, leading to weaker, less resilient regenerated skin and reduced treatment effectiveness.[77] Because resurfacing laser treatments rely on efficient wound healing, stress-induced impairments can prolong recovery and compromise skin regeneration, and integrating stress management into pre- and post-treatment care may help optimize outcomes from these scar treatments.

Chronic stress impairs fibroblast function, disrupts inflammatory signaling, and weakens tissue regeneration, reducing the effectiveness of treatments like subcision, CROSS, dermabrasion, surgical revision, and laser resurfacing.[3,68] Because effective scar treatments depend on collagen synthesis and well-regulated healing, stress-related disruptions can slow recovery, increase complications, and worsen aesthetic outcomes. Managing psychological stress as part of scar treatment could enhance healing efficiency and support better collagen formation. Given these challenges, developing strategies to mitigate stress-related barriers is essential for improving scar treatment outcomes. The following sections will explore these approaches in more detail.

The Paradox of Glucocorticoids in Inflammation and Scar Treatment

The use of GCs in scar treatment presents an apparent paradox, as they can both suppress and, under certain conditions, exacerbate inflammation.[36] In controlled doses, intralesional corticosteroids effectively regulate excessive inflammation by mimicking the body's acute stress response.[78] However, with chronic exposure, as occurs during prolonged psychological stress, GCs can desensitize GRs, sustain cytokine activity, and impair tissue repair.[36,38] For hypertrophic scars, corticosteroid injections reduce fibroblast activity and collagen synthesis, helping to minimize scar thickness.[78] In contrast, treating atrophic scars requires stimulating collagen production through interventions like subcision, laser resurfacing, and chemical reconstruction, all of which depend on active fibroblast function.[79] Chronic stress may hinder these interventions by impairing fibroblast activity and reducing collagen production.[69]

Given that stress disrupts the balance between collagen synthesis and degradation, one might wonder whether this effect could be beneficial in hypertrophic scarring, where excess collagen is the primary concern. While this may seem plausible in theory, chronic stress broadly impairs wound healing by exacerbating inflammation, disrupting fibroblast activity, and promoting abnormal collagen deposition.[80] Though GCs are widely used to manage inflammatory skin conditions, chronic use is associated with adverse effects such as dermal atrophy and decreased collagen levels.[35] Ultimately, while corticosteroids remain a valuable tool in scar management, dysregulated GC signaling induced by chronic stress is largely detrimental to healing. Managing psychological stress in patients undergoing scar treatments, whether for hypertrophic or atrophic scars, is essential to optimize healing and improve treatment outcomes.

Psychological Stress, Mental Health, and Scar Treatment Efficacy

As established, psychological stress has a significant impact on wound healing and collagen formation, making it a critical factor to consider in scar treatments, initiating a cascade of physiological responses.[65] In addition to its physiological effects, psychological stress also disrupts behavioral pathways, including sleep, nutrition, and overall health behaviors.[81,82] Patients under significant stress may struggle with treatment adherence, neglect proper wound care, and engage in behaviors that further delay healing.[11] Stress-related conditions like anxiety and depression exacerbate these issues, creating a cycle that impairs recovery and increases complication risk.[19] Ultimately, poor adherence compromises treatment outcomes, prolonging healing and reducing the effectiveness of scar interventions.

The relationship between stress and scarring is bidirectional: while stress impairs healing, scars themselves can perpetuate psychological distress, creating a detrimental feedback loop.[83] Scars frequently impose a psychosocial burden, triggering feelings of stigmatization and distress, and serving as persistent reminders of trauma.[84] This harmful loop further highlights the need for scar treatments that address both physical and psychological dimensions, ensuring more comprehensive healing.

Mental health critically influences wound healing and skin health by modulating the body's stress response systems, an increasingly important fact as he global prevalence of mental health disorders, particularly anxiety and depression, has markedly increased, with incidence rates rising from 1990 to 2019.[3,85] This trend raises concerns regarding the influence of psychological stress on wound healing and scar formation. Chronic psychological stress, often present in anxiety and depression, prolongs activation of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis.[86,87] Prolonged activation elevates glucocorticoid levels, disturbing the balance between inflammation and tissue repair.[88] Mental health disorders, especially depression, are also linked to immune dysregulation, with elevated levels of pro-inflammatory cytokines like IL-1, IL-6, and TNF-α.[89] Anxiety disorders further impair healing by increasing cortisol levels and suppressing immune function.[90] Notably, one study reported that patients with higher depression scores were significantly more likely to present with non-healing wounds after one month, underscoring mental health's direct impact on healing.[90] The increasing global incidence of anxiety and depression further emphasizes the need to address psychological factors in wound healing and scar management.

Strategies to Mitigate the Impact of Stress

Given the strong connection between stress, mental health, and scar healing, integrating psychological support into scar treatment protocols is essential.[91,92] Simple interventions, such as relaxation techniques, stress management education, and brief mindfulness exercises, can be readily integrated into clinical practice.[93] For instance, clinicians can guide patients through brief breathing exercises during visits or offer resources for mindfulness practices at home.[93] Additionally, evidence-based psychological interventions, such as cognitive-behavioral therapy and mindfulness-based stress reduction, have shown promise in reducing stress and improving healing outcomes.[94] Such approaches assist patients in managing the emotional burden of scar treatment, improving adherence and reducing stress-related impairments in healing.

Identifying patients at risk of heightened stress is crucial for delivering timely and effective interventions.[92] Routine stress assessments, access to stress management resources, and timely mental health referrals are key strategies for identifying and supporting high-risk patients.[92] Incorporating stress check-ins and fostering open conversations about emotional health during medical appointments could help patients manage stress in a practical, accessible manner. A comprehensive approach that addresses both physical and psychological aspects of healing enhances adherence to treatment protocols, reduces stress levels, and improves healing outcomes.

Systematic evaluation of stress impact on healing requires validated assessment tools, such as the Perceived Stress Scale (PSS), the State-Trait Anxiety Inventory, and the Psychological Stress Measure.[95–97] One study examined the relationship between perceived stress and wound healing speed following a standard punch biopsy, finding that patients with higher stress scores on the PSS were associated with slower healing.[97] These findings suggest that stress-induced delays in wound healing are primarily mediated by cortisol elevation, rather than behavioral factors.[97] This underscores

the importance of integrating validated stress assessments in research to clarify the biological mechanisms by which psychological stress impairs tissue repair.

Discussion and Limitations

To date, there exists growing evidence supporting the connection between mind and body, particularly in how psychological factors influence physical healing.[3,7] Chronic stress activates neuroendocrine and immune pathways that impair fibroblast function and delay tissue repair, mechanisms central to scar formation and treatment efficacy.[6,8]

While these biological effects are well-established in wound healing research, few studies have specifically examined whether mitigating psychological stress can enhance scar treatment outcomes. This gap represents an important opportunity for further research. Randomized controlled trials and longitudinal studies are needed to evaluate how stress-reduction strategies, such as mindfulness-based interventions or cognitive-behavioral therapy, might enhance scar treatment outcomes.

Additionally, further mechanistic studies are warranted to examine how psychological modulation influences fibroblast activity, cytokine signaling, and collagen dynamics within the scar healing process. Addressing these gaps would inform more effective, integrative treatment approaches that simultaneously support physical repair and patient mental well-being. Ultimately, embracing a comprehensive, biopsychosocial model of scar care has the potential to advance the field significantly. By recognizing the interplay between psychological stress and physiological healing, clinicians can design more personalized and effective scar treatment strategies.

Conclusion

This review highlights the complex and multifaceted role of psychological stress in impairing wound healing and reducing the efficacy of scar treatments. Chronic stress activates the SNS and disrupts HPA axis regulation, leading to prolonged exposure to catecholamines and GCs.[6,8] These disruptions impair fibroblast function, alter immune responses, and degrade extracellular matrix integrity, ultimately hindering collagen synthesis and tissue remodeling.[6,8]

Stress-induced alterations diminish the effectiveness of both collagen-stimulating interventions (eg, subcision, chemical reconstruction, laser resurfacing) and treatments reliant on coordinated wound healing (eg, surgical scar revision, dermabrasion). A growing body of evidence supports these mechanisms, demonstrating the detrimental effects of stress hormones on skin barrier function, fibroblast proliferation, and collagen production. Furthermore, the bidirectional relationship between scarring and psychological stress complicates patient care, as scars can exacerbate psychological distress, further impairing healing in vicious cycle. This relationship emphasizes the need for comprehensive strategies that address both physical and emotional health.

Given the rising prevalence of stress-related disorders, integrating psychological interventions into scar management is both necessary and timely. Evidence-based approaches, such as cognitive-behavioral therapy, mindfulness-based stress reduction, and validated stress assessment tools, offer practical strategies to mitigate stress-related impairments in wound healing and improve treatment outcomes. Future research should prioritize high-quality clinical trials that specifically assess the impact of psychological interventions on scar treatment outcomes. Additionally, mechanistic studies examining how stress modulation affects fibroblast function and extracellular matrix remodeling are essential for refining therapeutic strategies.

Adopting a holistic, patient-centered approach that integrates both physiological healing and psychological care has the potential to transform scar treatment practices. By incorporating mental health support into standard care protocols, clinicians can enhance physical healing, improve patient adherence, and support overall quality of life.

Abbreviations

HPA axis, hypothalamic-pituitary-adrenal axis; GC, glucocorticoid; MMP, matrix-metalloproteinase; ECM, extracellular matrix; SNS, sympathetic nervous system; NE, norepinephrine; β2ARs, β2-adrenergic receptors; GR, glucocorticoid receptor; FKBP5, FK506-Binding Protein 5; IL-1, interleukin-1; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; FN-β, interferon-beta; IFN-γ, interferon-gamma; subcision, subcutaneous; CROSS, chemical reconstruction of skin scars; (CO_2), carbon dioxide; ER:YAG, erbium yttrium-aluminum-garnet; PSS, Perceived Stress Scale.

Disclosure

The author(s) report no conflicts of interest in this work.

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