

Review of the relationship between stress and wound healing: part 1

While it has been suggested there is a link between stress and delayed wound healing, less is known about the role of pain as a contributor to stress. This paper reviews the evidence for this from studies of acute, surgical and chronic wounds

stress; pain; wound healing; acute wounds; surgical wounds; chronic wounds

Wound pain can cause suffering and distress. The effects of frequent dressing changes can interfere with daily routines, while loss of sleep, restricted mobility, pain, malodour and the physical and psychological effects of different wound treatments can reduce quality of life.¹ Chronic wounds, in particular, are strongly associated with reduced quality of life.²

This article reviews the evidence for the relationship between stress, pain and wound healing, focusing on research involving acute and chronic wounds in both experimental and naturalistic (observation of naturally occurring wounds) settings. Pain and stress comprise complex physiological, psychological and social interactions (Table 1). In this paper, pain and stress are both described as biopsychosocial concepts.

Search methodology

Studies were identified using PubMed, CINAHL, BNI, Academic Search Premier and PsycInfo databases. A follow-up search of references from articles already obtained was used to identify additional relevant studies. The literature search covered the period from 1988 to June 2009.

The following terms were searched both separately and in various combinations as keywords anywhere in the article: wound healing; psychological; physiological; stress; delayed healing; acute; chronic; wounds; pain; management; assessment.

Studies were included using the following criteria: the use of stress and pain measures; inclusion of male and/or female participants; patients with chronic wounds, surgical wounds or biopsy wounds; reviews of the relationship between psychological stress and wound healing; publication in English-language, peer-reviewed journals.

Studies were excluded if they involved the use of animal subjects; were case studies; or were review articles of specific dressings.

Twenty-six papers met the inclusion criteria. Of

these, a sub-sample of 16 studies was included in the categories of studies of biopsy wounds, surgical wounds and chronic wounds. KS searched for and selected the articles for inclusion, and this was confirmed by VM and DU.

Pain cycle

Pain is a complex and multidimensional experience. The two main types of pain are nociceptive and neuropathic.

Nociception occurs when sensory receptors (nociceptors) communicate information regarding damage or trauma from the body to the central nervous system, where it is interpreted by the brain as pain.³ Nociceptive pain can be acute or persistent (chronic) and is generally localised to the wound and surrounding tissue.⁴

Neuropathic pain is a consequence of nerve damage, resulting in abnormal transmission of pain to the central nervous system.⁵ Neuropathic pain is commonly persistent and can become independent of the initial injury or damage.⁴

Wound pain can result from the wound itself and can also be caused by some wound treatments. Patients with unresolved wounds may experience both chronic pain and the acute pain associated with dressing change. For example, patients can experience nociceptive pain (persistent aching) due to tissue damage and neuroceptive pain (abrupt stinging or stabbing pain) caused by nerve damage.⁶ In addition, interventions such as dressing removal, wound cleansing, debridement and inappropriate dressing selection can contribute to wound-related pain. Dressing removal and wound cleansing have been reported as the most painful experiences associated with wounds.^{7,8}

Pain can contribute to stress and other negative emotional states such as anxiety, fear and depression.³ Although the relationship is complex, it has been suggested that anxiety leading to stress can decrease one's pain threshold and reduce pain tolerance.³

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Declaration of interest

This review was
commissioned by
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Table 1. Examples of biological, psychological and social factors that contribute to stress and pain

Psychological factors	Biological factors	Social factors
Negative emotional associations (for example, anticipation of pain at a dressing change)	Sustained cortisol release leading to a depression in immune functioning	Poor availability and quality of social support networks and personal relationships
Previous experience of painful and stressful events	Chronic pain occurrence as a result of both increased cortisol levels ⁵ and wound treatments	Poor mobility and activity levels
Individual differences in perception and appraisal of a painful or stressful event	Increased heart rate, respiration rate and blood pressure	Negative social comparisons with other patients at different stages of recovery
Poor strategies of for coping with pain and stress	Lowered immune system functioning, which if prolonged can result in a detrimental excessive immune response (sympathetic nervous system arousal)	Negative environmental factors (for example, hospital/clinic attendance versus home visits)

In addition to underlying physiological factors, the perception of pain is influenced by psychological, emotional, cognitive and social factors — for example, anticipation of pain before wound treatment and patients' existing strategies for coping with pain coping.⁹

Impact of pain on wound healing and psychological wellbeing

It has also been suggested that pain itself may have a negative impact on wound healing. McGuire et al.¹⁰ revealed that, in a sample of patients undergoing gastric bypass surgery, persistent post-surgery pain was an important predictor of healing time. Patients who rated their pain as <8/10 on the first two days post-surgery experienced faster healing compared with those who reported more intense pain post-surgery.¹⁰

Chronic wound pain has been related to poor adaptation to living with a wound, such as depression and low self-esteem.¹¹ In patients with leg ulcer pain, worries and frustrations about the wound and lack of self-esteem as a result of the symptoms can have a negative impact on psychological functioning.¹² Although both patients and practitioners understand that pain is an accepted feature of chronic wounds, both as a consequence of failure to heal and as an aspect of treatment, it causes distress to the patient, which may delay healing.⁴

Stress

The term 'stress' often refers to the consequences of the failure of the human body to respond appropriately to emotional or physical threats.¹³ Stress can be described as a multidimensional concept as it comprises physiological, psychological and social factors.

Physiologically, stress can lead to raised levels of the hormone cortisol,¹⁴ which, if prolonged, increases the heart rate, raises blood pressure, and affects immunity and inflammatory responses in the body. Sustained cortisol release can lead to myopathy, weakness, fatigue and a suppressed immune system.⁵ A reduction in the levels of inflammatory cytokines and enzymes involved in tissue repair will inhibit the regeneration of endothelial cells, resulting in delayed wound healing.⁶ Furthermore, prolonged immune suppression might progressively decrease, giving way to the opposite effect: an excessive immune response in which the immune system attacks its own body,⁵ which could potentially result in further damage to the healing process. This offers a plausible explanation of how reduced rates of wound healing occur with pain-induced stress.¹⁵

It has been suggested that psychological factors, including stress and anxiety, play a role in the perception of pain; for example, under conditions of increased stress, anticipation of pain at dressing removal can lead to an increase in pain intensity,⁵ particularly if the patient has experienced this on a previous occasion.

Using appropriate dressings to facilitate a reduction in the level of pain experienced by patients could potentially minimise stress.¹⁶ For example, a multinational survey on pain at dressing change found that the use of dressings designed to avoid pain and peri-wound maceration was beneficial to patients.¹⁷

Psychologically, stress may increase the likelihood of patients making cognitive errors or negative appraisals — for example, if a patient feels unable to cope with a wound treatment, such as a dressing change, they may always perceive it as a negative experience. However, it is rational to perceive a dressing removal as an unpleasant experience if it has been painful in the past, although this can be detrimental to healing as it could lead to avoidance of treatment.¹⁸

Negative emotional responses to treatment may affect biological and behavioural responses, such as a prolonged fight-or-flight response, which may have a further negative effect on the emotional response to pain, producing a continuous cycle.¹⁹ Therefore, if wound treatment leads to increased anticipatory pain, stress and avoidance behaviour, delayed wound healing could occur as a consequence.

The relationship between stress and wound healing

A number of studies have suggested there is a link between stress and delayed wound healing.^{14,15,20-28} For example, stress is associated with slower or delayed wound healing in stressed older adults, adults with leg wounds and surgical patients.²⁹

Studies of biopsy wounds

An association between psychological stress and delayed wound healing has been demonstrated in studies of biopsy wounds.^{14,15,20-24}

For example, a study by Kiecolt-Glaser et al.³⁰ looked at the impact of hostile marital interactions on pro-inflammatory cytokine production and the healing of experimentally induced blister wounds. A sample of 42 married couples were required to attend two hospital visits where they were each given a blister wound. During the first admission, couples were involved in a discussion about social support and their relationship. In the second admission, they were interviewed by the investigator about conflict in their relationships and how it could be resolved.

Fluid from the wounds was obtained at 4, 7 and 22 hours after they had been administered, and blood samples were taken in the morning of the first admission. Participants also completed the Rapid Marital Interaction Coding System, which discriminates between high and low hostile behaviours.

It was found that blister wounds healed more slowly following conflict interviews than after the social support discussions. Furthermore, couples categorised as high-hostile experienced slower wound healing during both discussions when compared with low-hostile couples.

In addition, a more recent study examined the effect of an emotional disclosure intervention on participants who had been given a biopsy wound. Participants who wrote about a traumatic and upsetting experience in their life and disclosed thoughts and feelings they had not previously shared with anyone else had significantly smaller punch biopsy wounds at 14 and 21 days when compared with a control group (who wrote about time management).²⁰

There is considerable evidence that interventions such as emotional disclosure, which reduce both procedural and outcome stress associated with surgery, can produce beneficial effects on a range of recovery indices, including pain, mood and length of hospital stay.²⁰⁻²² Weinmann's study suggests there is a link between stress and wound healing and highlights the potentially important role of implementing stress management interventions before and possibly during the wound-healing process.

Similarly, in a study investigating the potential benefit of implementing stress management interventions during the wound-healing process, it was

hypothesised that outward and inward anger expression and lack of anger control was associated with delayed wound healing.²³ In a sample of 98 participants it was found that individuals exhibiting lower levels of anger control were more likely to be categorised as slow healers. These participants exhibited higher cortisol reactivity during administration of the biopsy wound, which was in turn related to a longer healing time.²³ These findings suggest that the ability to regulate the expression of anger has a clinically relevant impact on wound healing, and that there might be a role for anger management interventions should evidence point to their effectiveness.

However, it has also been demonstrated that the brief, predictable and mild stress experienced as a result of academic examinations can have significant consequences for wound healing. In a study by Marucha et al.,¹⁵ 11 dental students received two punch biopsy wounds on the hard palate of their mouth (the first during their summer holiday, the second three days before an important examination); each participant therefore served as their own control. Assessment of healing included daily photographs and foaming response to hydrogen peroxide. During the examination period, wounds took an average of three days (40%) longer to heal completely, while production of interleukin-1 beta declined by 68% during this period, providing evidence of one possible immunological mechanism.

Building on this evidence, Ebrecht et al.¹⁴ investigated the association between perceived stress and impaired wound healing. To minimise inter-individual variation in cortisol levels due to gender, only males were recruited. Each participant was given a 4mm punch biopsy wound monitored by the use of high-resolution ultrasound scanning. Participants completed questionnaires on perceived stress (Perceived Stress Scale, PSS) and health behaviours (General Health Questionnaire, GHQ-12).^{31,32} Samples of saliva for cortisol assessment were collected after awakening, and at two weeks before, directly after and two weeks after the wound was administered. Results showed a significant negative relationship between speed of wound healing and both PSS ($r=-0.59$; $p<0.01$) and GHQ-12 ($r=-0.59$; $p<0.01$) scores at the time of wounding. The relationship between cortisol response in the morning of the day following administration of the wound and the speed of wound healing was found to be negatively correlated: cortisol levels increased, while the speed of healing decreased ($r=-0.55$; $p<0.05$). However, the association between health behaviours (such as alcohol consumption, exercise, healthy eating and sleep influences) and healing speed was not significant and these factors were not found to be associated. These findings suggest that stress has a considerable influence on wound healing, and that elevated cortisol levels, rather than health

behaviours, play a role in this effect.

A study by Glaser et al.³³ found that, after being given a blister wound, participants who had reported higher levels of stress on the PSS produced significantly lower cytokine levels and a higher number of adverse life events compared with participants who had high cytokine levels. Furthermore, participants with low cytokine levels also had higher levels of salivary cortisol than those with high cytokine levels. These findings suggest that stress can delay the appearance of pro-inflammatory cytokines early in the wound-healing process, which could have a detrimental effect on wound repair.

In contrast to previous biopsy wound healing studies, Kiecolt-Glaser et al.²⁴ investigated the effect of long-term, naturally occurring, psychological stress caused by caring for a relative with Alzheimer's disease on healing. Thirteen women caring for relatives with Alzheimer's disease and a control group were given a punch biopsy wound on the non-dominant forearm and completed the 10-item PSS³¹ at the time and one week later. Wounds were assessed using photography and hydrogen peroxide, and were defined as completely healed when the site no longer foamed after peroxide application. Caregivers reported significantly more stress than the controls, and wound healing took an average of nine days longer in the caregivers than controls.

These findings support the notion that psychological stress can impair wound healing, and in particular in carers of patients with a long-term illness such as Alzheimer's disease. This suggests that those with chronic stress can have impaired wound healing. However, the findings should be treated with caution as the sample size is modest, which limits the extent to which these findings can be generalised outside of the study population, and would therefore need to be replicated in other settings.

Studies on surgical wounds

While biopsy wound studies may provide a basis for understanding the relationship between stress and wound healing, they are not necessarily representative of the relationship between stress and chronic wound healing. One way of addressing this is to explore the literature on surgical outcomes. Although surgical wounds are also considered to be acute, research findings in this area may be more robust compared with studies involving experimentally induced wounds.

Wound healing is a critical outcome in surgery.^{23,25} Poor healing can result in wound infection or complications, a prolonged hospital stay, increased patient discomfort and delayed return to activity.²⁵ Consequently, interventions that are aimed at reducing the stress of surgery and that putatively improve wound healing are of interest in clinical practice. Holden-Lund examined the effects of

relaxation with guided imagery (RGI) audiotapes on wound healing.²⁶ (RGI tapes are designed to guide the patient's imagination toward a relaxed but focused state.) Surgical patients were randomly assigned to either the RGI group or control (no tapes). Patients in the RGI group demonstrated significantly less anxiety, lower cortisol levels (one day following surgery) and less surgical wound erythema than the controls. It is suggested that the RGI tapes brought about a reduction in stress, which was closely associated with healing.

Similarly, in a study by Broadbent et al.,²⁵ a sample of 47 patients with an inguinal hernia were given the 10-item PSS³¹ to assess preoperative stress. Wound fluid was collected from patients over the first 20-hour postoperative period. Wound healing was assessed by levels of interleukin-1, interleukin-6 and matrix metalloproteinase-9 in the fluid. It was found that greater preoperative stress significantly predicted lower levels of interleukin-1 in the wound fluid. Greater anxiety about the operation were associated with lower levels of matrix metalloproteinase-9 in the wound fluid as well as more painful, poorer and slower recovery. These results also suggest that, in clinical practice, interventions to reduce patient stress may improve wound repair and healing, and facilitate recovery following surgery.

In terms of the impact of pain on surgical outcomes, Beilin and Shavit³⁴ demonstrated that patients who self-administered epidural analgesia following abdominal surgery experienced less severe postoperative pain, measured by a visual analogue scale (VAS), when compared with patients using opioid pain relief (which can suppress the immune system, making it more susceptible to infection). Patients who used the self-administered epidural analgesia also displayed a reduced suppression of lymphocyte proliferation and pro-inflammatory cytokine response during the postoperative period.

These findings suggest that using epidural analgesia as postoperative pain relief may lower the risk of postoperative infection due to the reduced suppression of the immune system. Furthermore, the pro-inflammatory cytokine response may have contributed to a reduction in postoperative pain and, potentially, the prevention of chronic pain.

Although this study did not measure wound healing specifically, these findings suggest that when patients may experience less compromised immune function when they have control over the mode of pain relief. Further research could examine the potential impact of different types of analgesia and modes of pain relief on the speed of wound healing.

Studies on chronic wounds

The findings of the following studies provide empirical support for the relationship between stress and delayed healing in chronic wounds. A study by

Jones et al.²⁷ explored the prevalence of stress, including anxiety and depression, in 190 patients with chronic venous leg ulceration across nine trusts in the northwest of England. The hospital anxiety and depression scale (HADS)³⁵ was used to assess patients for the presence of anxiety and depression. Fifty-two patients (27%) scored above the cut-off for categorisation as depressed, and 50 patients (26%) scored above the cut-off for anxiety. The two symptoms which appeared to be most associated with anxiety and depression were pain and malodour. The investigators concluded that wound care should be refocused for patients living with a chronic wound when cure is not an option, and that psychological factors, including anxiety and depression, should be key considerations in the assessment and review of patient care.

Cole-King and Harding²⁸ also examined the relationship between the healing of chronic wounds and anxiety and depression. A sample of 53 male and female participants was included in the study. Wound healing was rated using a five-point Likert scale, and anxiety and depression were measured using the HADS. Psychological and clinical wound assessments were conducted, with the investigators and participants blinded to the results of the other assessments. The relationship between the healing of chronic wounds and anxiety and depression was statistically significant: delayed healing was associated with a higher mean HADS score ($p=0.03$), demonstrating that symptoms of both depression and anxiety were associated with chronic wound healing. It should be acknowledged, however, that a causal relationship between stress and delayed wound healing cannot be inferred from these findings as other factors, such as physical or social limitations resulting from the wound, may play a role in this relationship.

With regard to the impact of pain on wound healing, a multinational survey of the assessment of pain at dressing removal compared the impact of different dressings in a sample of 3,034 patients with a variety of chronic wounds. At visit one, pain levels (measured by the VAS) increased during removal of all types of traditional adhesive-based dressings.¹⁷ In comparison, pain ratings significantly decreased ($p=0.01$) at visit two after patients had been treated using soft-silicone adhesive dressings. These results demonstrate that using dressings that cause minimal pain on removal can benefit patients' experience of wound care. Further, the reduction in pain, and thus its effect as a stressor, may potentially reduce healing times.

Overall considerations

The findings of these studies show that methods of assessing stress during wound treatment would benefit the healing process by enabling the practitioner

to understand the patient's individual needs for minimising stress. Practitioners should pay particular attention to both physiological and psychological aspects when delivering wound care. For some patients, psychological treatments, such as emotional disclosure, in addition to wound treatment, may help improve quality of life, relieve subjective distress and potentially also promote wound healing. It would be beneficial for patients if practitioners were to take account of the role that stress plays in wound healing, particularly in leg ulceration, where stress may increase the incidence of wound recurrence.

Evidence for the role of pain, however, is limited in the above studies. Theoretically, it would seem that pain itself can be viewed by patients as a stressor, thereby contributing to delayed wound healing. Despite the limited evidence, it has been suggested that the management of pain is as important as the treatment of the wound itself,³⁶ as this could help reduce in stress during wound care.

Discussion

Overall, the studies of biopsy wounds, surgical wounds and chronic wounds included in this review provide evidence to support the relationship between stress and wound healing. It would appear from the literature that stress can affect the healing of different types of wounds, both psychologically and physiologically. For example, both experimental and naturalistic studies documenting the use of emotional disclosure interventions and relaxation techniques during wound care were found to relieve patients' anxiety and stress, which increased the speed of wound healing when compared with the controls. Furthermore, it has been highlighted that patients who exhibit poor anger control or engage in hostile interactions can experience a delay in wound healing, when compared with patients categorised as low-hostile. This suggests that anger management interventions may be beneficial. Further research is needed in this area.

Although the results of studies of biopsy and surgical wounds support the notion that psychological stress can delay acute wound healing, it is not possible to determine the role of stress in the delayed healing of chronic wounds from them. Indeed, evidence of the mechanistic underpinnings of the relationship between stress, pain and chronic wound healing is limited, and most of the evidence for a causal link between stress and wound healing comes from studies of acute wound healing. Several studies demonstrated physiological changes in the levels of pro-inflammatory cytokines and salivary cortisol in patients with acute and chronic wounds. Such changes can suppress the immune system and have detrimental effects on the wound healing process. However, chronic wounds do not necessarily follow

the same healing process as acute wounds, particularly in response to stress.

Taken together, the studies suggest that stress and anxiety are detrimental to the wound healing process. Both chronic pain and the anticipation of pain can generate distress. If this iatrogenic pain is viewed as a stressor, then it may have detrimental effects on the healing of acute and chronic wounds. This needs to be taken into account when managing all aspects of treatment.

Few studies have looked specifically at the role of pain in this relationship. White¹⁷ highlighted that different types of dressing can contribute to pain relief, and Beilin and Shavat³⁴ showed that different

types of analgesia and mode of delivery of pain relief may mediate immune functioning. Further investigation in the domain of wound healing would provide a basis for understanding the role of wound-related pain in healing rates of acute and chronic wounds.

The second part the literature review will examine current physiological and psychological measures of both pain and stress that can be implemented in clinical practice as part of the wound assessment and management process. As wound pain can contribute to psychological stress, measurement and successful management of wound pain could help minimise stress in patients, and

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