# The impact of psychological stress on wound healing: a theoretical and clinical perspective

KEY WORDS
- Allostatic load
- Allostasis
- Psychology
- Stress

The impact of psychological stress has been the subject of controversy for many years, with its true impact yet to be clearly delineated. Two seminal theories laid the foundation of our current understanding of the impact of stress on wound healing and form the basis for many clinical investigations. Challenges associated with the study of stress and wound healing include differences in definitions as well as pragmatic challenges quantifying stress. This article critically discusses the original theories related to stress and physical health in the context of wound healing, as well as contemporary evidence indicating the impact of stress on the normal wound healing response.

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The biopsychosocial model of health, initially proposed by Engels (1977) stated that physical health is influenced by a combination of biological, psychological and social factors. According to McInerney (2018), this theory was paramount in the paradigm shift leading to a departure from strict adherence to the biomedical model to psychosocial considerations in clinical decision making. This theoretical model later gained support from the World Health Organization (WHO) (1986) who stated that 'health is a positive concept emphasising social and personal resources, as well as physical capabilities'. The change in focus from a purely biological stance on disease leads to further research and the development of psychosocial considerations such as those recommended by the National Institute for Health and Care Excellence (NICE, 2007) which are not solely in the domain of specialists but also of general clinicians in all settings (McInerney, 2018).

Associations between stress and physical health have been delineated, including its correlation with poor cardiovascular health, metabolic dysfunction (Juster et al, 2010), altered immune function and, links have been demonstrated between stress and deleterious behavioural traits, such as smoking and poor diet (Takahashi et al, 2018). Stress within the context of wound care has been explored and relationships between stress, impaired healing and biomarkers related to healing established (Walburn et al, 2009; Godbout and Glasser, 2006).

This discussion will focus on studies exploring the impact of chronic stress on non-healing chronic wounds as these are frequently the result of abnormal extensions of the inflammatory response and therefore more susceptible to immune-endocrine changes induced by stress (Walburn et al, 2009).

## DEFINITION OF STRESS AND HOW STRESS IS MEASURED

Cohen et al (1997) defined stress as, *'a process whereby environmental demands exceed a person's individual perceived ability to cope resulting in behavioural and physiological changes'*. More recently different types of stress have been described by Sergestrom and Miller (2004) including acute stressors, for example, a short traumatic experience, or chronic stresses associated with disease processes or long-term social troubles such as homelessness or relationship issues, as well as individual perceptions of stress. Sergestrom and Miller (2004) proposed that alternative stress aetiologies are linked to a different impact on immunity and by extension differing implications for comorbidities such as wounds. However, the varying conceptual interpretations of psychological stress create difficulty comparing studies into the impact of stress on disease

**Figure 1. Psychophysiological feedback loop (adapted from Crosby, 1988)**

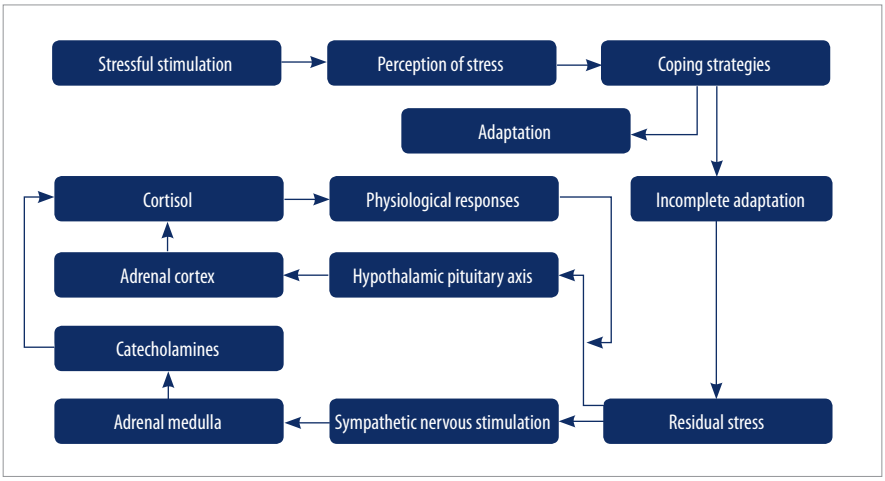
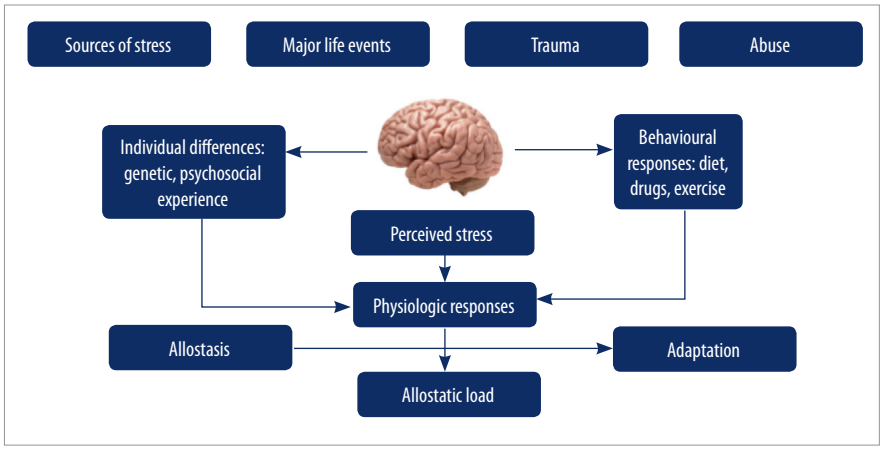



**Figure 2. The allostatic load model (adapted from McEwen, 1998)**




processes and, ultimately establishing causal relationships between stress and disease (Walburn et al, 2009). Evaluating the impact of stress is also complicated by the notion of differing stress typologies associated with 'chronic stress' which may have different impacts on health, notably chronic interpersonal social stressors, such as homelessness or domestic abuse, are particularly health damaging both physically and mentally (Slavich et al 2010, Sheets and Craighead, 2014).

Stress is measured in studies using a variety of scales including but not limited to the positive and negative affect schedule (PANAS) (Thompson, 2007), the self-perceived stress questionnaire (SPSQ) (Levenstein et al, 1993) and the profile of mood states (POMS) (Nyenhuis et al, 1999). In addition to psychometric scales, physiological measurements such as punch biopsies have been used in the context of stress-wound healing research in both acute and chronic wounds (Walburn et al 2009). Despite the availability of scales and biological measures, Epel et al (2018) discussed that currently there is no consensus on how stress should be measured for research purposes. This is in part due to the multi-dimensional nature of stress affecting patients at social, physiological and psychological levels making assessment challenging (Epel et al, 2018).

From a physiological perspective, acute physiological stress in wounds is characterised by protective immuno-enhancing changes in leukocyte concentrations at the site of wounding preparing the body for microbiological contamination (Vileikyte, 2007). Whereas chronic stress is associated with measurable increases in inflammatory cytokines that can prolong wound healing times (Christian et al, 2006). However, controversy exists as to whether it is a physiological change, or the behavioural changes associated with stress (i.e poor diet or little exercise) that may be both the cause of the increase in both inflammatory markers and healing time (Christian et al, 2006; Gouin and Glaser, 2011). It has also been noted that physiological mediators of stress do not consistently correlate with subjective measures of stress as reported by patients, this is important in the assessment and measurement of stress demonstrating the need for both qualitative and quantitative measures when determining the impact of stress on disease (McEwen, 1998).

## MODELS OF STRESS AND HEALTH

The impact of chronic social stressors has been identified as being particularly harmful to health (Slavich et al, 2010; Sheets and Craighead, 2014) which is reflected in the early theoretical models which explore both social and physiological dimensions of stress. Two notable models include Crosby's physiological response model *(Figure 1)* and the Allostatic Load Model (ALM) *(Figure 2)* (Crosby, 1988; McEwen and Seaman, 1993).

## PHYSIOLOGICAL RESPONSE TO STRESS

Crosby's theory described a psychophysiological feedback loop, linking psychological stress to changes in immune responses and hormone concentrations (Crosby, 1988). He stated that the loop will persist until the stress signal is eliminated

by intervention or a change in circumstances. Crosby tested this theory experimentally by comparing rheumatoid arthritis symptoms and severity over time with scores taken from the daily hassles scale (DHS), state-trait anxiety inventory (STAI) and the visual analogue scale (VA) (Kanner et al, 1981; and Speilberger, 1970). Statistically significant correlations between the scores measuring stress and arthritis symptoms were found ($p<0.01$), Crosby (1988) thus concluded that emotional states brought on by stress were positively associated with arthritis symptoms.

The underlying assumption of the model is that an individual's ability to adapt to stress is the key factor in determining the impact that the stress will have on physiological changes, this adaption is described as either complete or a 'partial adaptation' (Crosby, 1988). However, this does not consider the impact that behavioural changes brought on by stress has on the physiological outcome measures used to validate the theory. Specifically, alcohol use, poor nutrition and poor sleeping patterns are associated with reduced immunity and in the case of wounds, impaired healing (Scholl and Langkamp-Henken, 2001; Berg et al, 2013; Baum and Poslunzny, 1999).

Crosby utilised multiple measures of stress which is not uncommon in stress-studies due to the lack of consensus on stress measurement (Epel et al, 2018). However, the use of the DHS, which became a focus for the analysis of the research findings by Crosby has been criticised due to its underlying assumption that more hassles directly correlates to 'more stress.' However; the individual 'hassles' specific impact on disease have not been validated, or the impact of the individuals ability to cope with the stressors, meaning their weighting in the scale is arbitrary and not a dependable measure of how much stress a person is experiencing or its correlation with symptoms (Cohen et al, 2016). Crosby (1988) argued that the impact of this was alleviated to an extent by the use of multiple stress measurement tools.

Crosby (1988) focussed clinical recommendations derived from the investigation of the model based on interventions to counteract the issues identified as causing the most stress for patients with rheumatoid arthritis (RA). These included patients feeling a 'lack of energy' and 'declining general health.' These sources of stress are arguably difficult to address clinically due to their non-specific nature and do not correlate with more contemporary studies into stress in patients with RA (Zautra et al, 2007).

In relation to individuals with chronic wounds, pain has been identified as being a significant source of stress in both chronic wound patients and RA patients (Woo, 2010). Pain has been established as an important cause of delayed healing due to inflammatory responses associated with it; as well as psychosocial impacts including behavioural changes secondary to pain-related stress, and social isolation created by mobility issues due to pain (Woo, 2012).

In summary, Crosby's (1988) model describes a relationship between unmanaged stress and the symptoms of RA due to increased stress hormone release. It does not, however, consider collateral factors that may impact physiological stress including damaging health behaviours, the direct impact of the disease process on physiological manifestations of stress as precipitated by pain or social isolation (Ebrecht et al, 2004).

## ALLOSTATIC LOAD MODEL

The ALM (McEwen and Seaman, 1993) built on earlier models such as Crosby's (1988) model but considered stress in a wider sense, describing the cumulative nature of stress and the impact that childhood experiences and genetics may have on how stress impacts disease.

The ALM is founded on two key concepts. 'Allostasis' which is the bodies response to stressful stimuli in which the body compensates for the stimuli using both chemical mediators of stress and behaviour changes. 'Allostatic load' is the second key concept and is the net result of both the stressful stimuli and an individual's ability to adapt to the stimuli. McEwen and Seaman (2009) describe a multitude of factors that contribute to an individual's ability to adapt and achieve an optimally reduced allostatic load; these include genetic, social and psychological factors.

Unlike older models of stress and health, allostatic load can be measured empirically using a range of biomarkers including; cortisol, interleukin-6, cholesterol, blood pressure and body mass index, incorporating elements of neuroendocrine, immune, metabolic, cardiovascular and anthropometric data creating a broad picture of an individual's health (Juster et al, 2010). Many biomarkers used to determine allostatic load and

those used in wound healing studies are the same, this indicates a further potential for biomarker monitoring to aid determining the prognosis of wounds or therapeutic impacts of wound healing treatments focussing on allostatic targets (Patel et al, 2016). The ALM has subsequently been used as a basis for investigative studies into the impact of stress, and high allostatic load has been found to be associated with greater physical pain, incidence of obesity and smoking (Crews, 2007; Goertzel et al, 2009; Fischer et al, 2009). These have all been demonstrated to be detrimental to wound healing (Guo and DiPietro, 2010).

Ultimately, the ALM has been of great clinical utility in identifying patients at risk of poor health due to their stressful lifestyles (Crews, 2007). The model also explains the discrepancy identified between perceived stress and the presence of biomarkers (McEwen, 1998). Notably, patients with a genetic predisposition to poorer allostasis or who have experienced a greater allostatic load at any given age due to stressful childhood experiences may have altered perceptions or physiological presentations of stress and therefore have altered biomarkers without perceptions of increased stress (McEwen and Seaman, 2009). In a review by Juster et al (2010), it was recommended that clinical interventions to reduce allostatic load need to be investigated. At present, clinicians need to remain aware that patient perceptions of stress are unlikely to be an adequate predictor of risks posed by allostatic load to their wounds (Crews, 2007).

Very few investigations on allostasis and wound healing have been conducted apart from animal studies on birds that indicated that chronic stress and high allostatic load reduced wound healing capacity (DuRant et al, 2016). Although the use of birds in stress physiology studies is popular (Lattin et al, 2012), they cannot be used as a substitute for human studies on patients with wounds susceptible to allostasis related wound complications, due to the well-documented differences in human bio psychophysiology (Ansell et al, 2012). Furthermore, positive results from animal models often fail to produce statistically significant results in human subjects (Sheridan et al, 2004).

More studies are needed investigating the impact of allostatic variance in patients with wounds, the impact it may have on co-morbidities and how it can be alleviated to improve clinical outcomes (Juster et al, 2010). Due to the measurable nature of allostatic load on physiological markers, it has also been suggested that patients could be targeted for intervention based on pre-clinically significant biomarker increases, potentially allowing the prevention of wound chronicity (Juster et al, 2010). The overlaps in biomarkers present in non-healing wounds and allostatic load may indicate the impact that stress has on wound healing and conversely the stress created by wounds, they represent a potential for empirical measurement of stress in future studies investigating stress and wound healing (Patel et al, 2016).

## CLINICAL EVIDENCE FOR THE IMPACT OF PSYCHOLOGICAL STRESS ON WOUND HEALING

The process of wound healing is complex and widely accepted to consist of four concurrent phases including haemostasis, inflammation, proliferation and epithelialisation (Brown, 2015). *Table 1* summarises the processes involved.

The pathophysiological impact of stress on acute surgical and punch biopsy wound healing has been studied by a number of authors (Chester et al, 2016; Meesters et al, 2018; Lucas et al, 2018). Interventions to reduce psychological stress in surgical wounds have also been indicated to improve wound healing and quality of life (Pinto et al, 2016). The literature on the impact of stress on chronic wound healing, however, is less prevalent. There is existing evidence from primary research and narrative reviews that have explored the impact of stress on venous leg ulcers and difficult to heal chronic wounds (Cole-King and Harding, 2001; Snyder, 2006; Peart, 2015).

A study carried out by Cole-King and Harding (2001) investigated the relationship between the hospital anxiety and depression scale (HAD) with wound healing rates. They found a statistically significant reduction in wound healing in patients with high HAD scores. This study demonstrated the clinically significant impact that psychological factors have on wound healing. Cole-King and Harding (2001) recommended further investigation into

**Table 1. The four processes of wound healing (Stacey, 2016)**

| Phase | Timeframe | Cells involved | Function | Cellular and biophysical events |
|---|---|---|---|---|
| Haemostasis | Instant | Platelets | Clotting to prevent blood loss | Vascular constriction, Platelet aggregation, degranulation, Thrombus formation |
| Inflammation | 1–4 Days | Monocytes, Lymphocytes, Neutrophils, Macrophages | Phagocytosis | Neutrophil infiltration, Monocyte infiltration, Lymphocyte infiltration |
| Proliferation | 4–12 Days | Lymphocytes, Macrophages, Angiocytes, Neutrophils, Fibroblasts, Keratinocytes | Wound bed filling, Wound closure | Re-epithelialisation, Angiogenesis, Collagen synthesis |
| Maturation | 21+ Days | Fibrocytes | Develop tensile strength | Collagen remodelling, Vascular maturation, Regression |

behavioural and pharmacological interventions to reduce the level of anxiety and depression in patients with potentially stress-induced delays in healing. The use of the HADs score to determine stress is common practice in both clinical and research practice (Lesage and Deschamps, 2012). However, the scale focuses on anxiety and depression related experiences and may, therefore, have failed to identify patients susceptible to wound complications due to allostatic load, which may not have necessarily been perceived by the patients (McEwen and Stellar, 1993). Ultimately, this could mean the study may have under-predicted the impact of stress on wound healing outcomes, and intervention based on improving HADs scores may only solve part of the problem.

Following this study, a literature review focussing on psychological models of health was conducted by Snyder (2006). This highlighted the causes of stress as reported by patients with wounds from qualitative phenomenological studies, in order to better understand the nature of stress in this patient group. Snyder (2006) identified that the biggest sources of stress in wounded patients are pain, odour and body image issues. Inability to carry out activities of daily living was also identified as a cause of secondary social isolation and feelings of hopelessness. This review is in contrast to the clinical study by Cole-King and Harding (2001) and suggests the target for clinicians aiming to reduce psychological burden should focus on physiological aspects of wound healing, such as pain management and odour reduction rather than behaviour focussed interventions (Renner et al, 2014). However, psychiatric input focussed on behaviour change has demonstrable benefits in patients with chronic pain, unresponsive to pharmacological treatment (Goesling et al, 2018). Further to the physiological contributors to stress, Snyder (2006) described the importance of coping strategies in wound healing. Notably, patients who received excessive social support were susceptible to adopting strategies of dependence, resulting in disempowerment, ultimately at detriment to their wound healing (Snyder, 2006). Snyder (2006) thus recommended that practitioners should be cautious of the impact that too much social support can have on patients perception of locus of control over their wound and; the importance of pain management in routine wound care to limit the psychological stress and psychosocial issues secondary to pain.

Peart (2015) presented a discussion of a patient case study with supporting literature to demonstrate that pain, body image and embarrassment were identified as major sources of stress. Peart (2015) recommended referral to psychology specialists for sources of stress outside of what might be considered routine wound management, for example, a patient who has issues related to body image.

## CONCLUSION

The prevailing view is that stress is a complex and ill-defined concept that impacts the nature of human experience at a social, psychological and physiological level (Epel et al, 2018). Theories of stress and illness have evolved. Initially stress was viewed as binary in its presence, with clinical manifestations such as poor wound healing a consequence of the physiological turbulence it creates (Crosby, 1988). The more recent opinion considers stress to be a dynamic experience manifesting intermittently which can be alleviated with varying success depending on genetic and social factors (Juster et al, 2010).

Clinical manifestations of unmanaged stress appear to be a consequence of both stress-induced

physiological changes, as well as behavioural traits adopted as a coping mechanism (McEwen and Seaman, 1993). Clinically, the impact of unmanaged stress has been demonstrated to increase the risk of non-healing, reduce quality of life, and adoption of health-damaging behaviours, indicating the importance of a multidisciplinary approach to wound healing (Cole-King and Harding, 2001; Walburn et al, 2009). The main sources of stress that have been identified include pain, odour and social isolation (Snyder, 2006). Currently, clinicians should consider the impact of stress-induced factors commonly associated with non-healing wounds, such as pain and odour for which there are well established interventions that can be included in treatment plans (Renner et al, 2014). Future studies should focus on the assessment of stress and interventions focussed on reducing the psychological burden on patients with wounds. WUK

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