Impact of psychological stress on wound healing for patients with diabetic foot ulcers

Hussam Eddine Saleh Itani, Nashat Ali Gandoura, Tauqeer Ahmed, Rima Mazen Ahmad

Diabetic foot ulcers are complex, chronic wounds that will often have a delayed healing trajectory. In the past the focus of treatment has been on the pathophysiology of DFUs. This article argues that there should be a greater focus on the impact of psychological stress when treating patients with DFUs. The authors show, through a review of the literature, that although acute levels of stress can have a positive effect on wound healing, long-term stress can delay wound healing in chronic wounds by raising levels of glucocorticoid and causing a down-regulation effect on the inflammatory response. The authors suggest that stress levels should be considered when planning treatment for patients with DFUs and that there should be more research into this area.

A diabetic foot ulcer (DFU) is a complication of diabetes and represents a significant medical, social and psychological risk to patients, as well as an economic burden to healthcare systems[1]. In his review Boulton[2], described the multifactorial aetiology of a DFU as the complication of uncontrolled hyperglycemia damaging the peripheral nerves and blood vessels. Bolton also stressed that this damage causes pain, tingling and loss of feeling that can easily allow injuries to go unnoticed, risking infection and ulceration.

As with all chronic wounds, the healing process for a DFU is governed by physiological and psychological factors[3]. Physiological factors include poor circulation, neuropathy, immune suppression, systemic diseases, aging and repeated trauma[4]. Psychological and behavioural factors range from psychological stress, mood swings, and changes in sleep patterns[5]. These factors contribute to the stagnation of wounds in the inflammatory phase thus preventing these wounds from healing, and leading to further complications such as pain, infection, malodour and leakage as well as an increased risk of amputation[6].

Complications can also boost the stress response that might be observed as an alteration in mood[7] and a disturbance in patients’ daily routine which has a negative impact on their quality of life[8].

The knowledge about the pathogenesis of DFU as well as treatment and prevention has improved in the past decade[9]. Nevertheless, there needs to be more research into the influence of psychological stress on the healing outcome of patients with DFU[10]. When planning clinical treatment protocols, not much attention is given to psychological factors despite the growing evidence provided about the impact of psychological stress on wound healing[11].

The main objective of this paper is to assess the relationship between psychological stress and the healing of DFUs.

Definition of stress
Stress occurs when individuals perceive that environmental strains exceed their adaptive capabilities resulting in behavioural and physiological changes[12]. According to Webster-Marketon and Glaser[13], the degree and duration of perceived environmental strains determine the level of stress response to a given event. Different forms of stress such as acute, chronic, psychological, or physical have different effects on the release of neuroendocrine hormones and immune functions[14].

Impact of stress on human health
Animal and human studies have demonstrated that stress increases the amount of neuroendocrine hormones released through two main pathways[15].
The hypothalamic-pituitary-adrenal (HPA) axis causes the release of glucocorticoids, while the sympathetic-adrenal-medullary (SAM) axis results in the release of catecholamine.

Existing research indicates that the release of glucocorticoid hormones, predominantly cortisol, causes the suppression of the inflammatory response, the modification of the cytokines profile, and the elevation of blood glucose levels. Catecholamine release causes the secretion of epinephrine and norepinephrine that results in alterations of the immune cell function and elevation in blood glucose level. The impact of these hormones affects health in many ways and can precipitate illnesses such as cardiovascular diseases, osteoporosis, arthritis, diabetes, certain types of cancer and also a delay in wound healing.

Two meta-analyses have been conducted to determine the relationship between stress and healthy human immunity. The first synthesised findings from 38 studies and the second synthesised findings from 75 studies. Both reviews included the study of speech tasks as acute laboratory stressors and medical examinations as short-term naturalistic stressors while long-term naturalistic stressors included divorce, bereavement, care-giving, and unemployment. Both meta-analyses concluded that consistent and prolonged stress resulted in an increase in circulating neutrophils and monocytes, a reduction in natural killer cell activity, and decreased lymphocyte proliferation and antibody production which resulted in delayed wound healing.

Research by Dhabhar on the body’s response to acute stress, found a positive impact of short-term stressors in activating the body’s physiological fight system that helps humans and animals to cope with challenges like fear, anger and other life-threatening burdens. In relation to acute wound healing, Dhabhar’s work showed an increase in leukocyte trafficking and cytokine gene expression at the wound site to manage foreign bodies and microorganisms in response to acute wound injuries.

These findings make it clear that human and animal response to short-term stress can have a therapeutic benefit, while prolonged stressful stimuli can lead to an imbalance in the body’s system that might contribute to the development of various diseases through different mechanisms.

**Impact of stress on the physiology of wound healing**

In their meta-analysis, Herbert and Cohen verified that perceived stress is directly associated with cellular and humoral immune deficiency, which has an impact on wound healing. Perceived stress is linked to wound healing through various routes involving increase in negative mood, alteration in immune function, prolonged inflammatory process, and changing behaviour such as inadequate sleeping patterns.

The physiological factor is revealed by the increase in glucocorticoid level that suppresses the wound healing processes. Glucocorticoid has a down-regulation effect on the inflammatory response and leads to the modification of cytokine profiles, mainly interleukin-1 (IL-1), IL-6, IL-8 and tumour necrosis factor. These cytokines play a critical role in the inflammatory and granulation phases of the wound healing stages.

Stalled wounds possess decreased growth factors and increased pro-inflammatory cytokines which lead to excessive matrix metalloproteinase activation. This outcome results in the breakdown of extracellular matrix molecules and growth factors, and inhibits the proliferation of fibroblasts and keratinocytes thus preventing the wound from healing.

**Stress and wound healing: gaps in the literature**

In the past decade, the interest in understanding the relationship between psychological stress and wound healing has increased tremendously. This has led to rapid growth in the amount of qualitative research done in this area. Qualitative research helps to understand human behaviour to build up the gap between scientific evidence and clinical practice. However, the subjective methodologies used to assess and interpret the collected data from such studies might hinder the accuracy of the outcome.

Sandelowski stressed that qualitative research is designed to study small groups thus the outcomes may not be accurate enough to generate statistical data. The triangulation of research methods, which combines qualitative and quantitative approaches, could help to fill in the gaps between the two methods and might help to obtain more reliable research outcomes.

A search of the literature indicates that studies addressing psychological stress and wound
healing have mainly concentrated on acute wound models\textsuperscript{[32]}. Acute and chronic wounds do not have the same healing trajectory, thus the impact of stress on chronic wound healing will be different\textsuperscript{[33]}. Future research should focus on the biological and behavioural factors mediating the association between psychological stress and healing of chronic wounds with different aetiologies\textsuperscript{[33]}.

**Psychological stress and diabetic foot ulcers**

The risk of developing a DFU has increased among patients with diabetes in North America, where prevalence rates might exceed 20\% and the rate of recurrence is also high. This increase has made the burden of DFU a major focus for the International Diabetes Federation\textsuperscript{[5]}.

The management of patients with DFUs requires long-term intensive care that might exceed five months\textsuperscript{[41]}. Such an extended period is associated with high cost and burden for patients, healthcare providers and healthcare systems\textsuperscript{[41]}. Long-term management and ulcer complications such as loss of mobility, pain, infection, and malodour create physiological stressors\textsuperscript{[41]}. Social isolation and fear of amputation lead to the development of psychological stressors\textsuperscript{[36]}. These stressors might lead to increased psychological stress among patients with DFU\textsuperscript{[41]}.

Although few studies have been done on the impact of stress on chronic wounds, particularly in DFU, more extensive work has been undertaken on biopsy and surgical wounds to provide evidence on the relationship between stress and wound healing\textsuperscript{[34]}. The available literature shows strong evidence relating to the psychological and physiological effect of stress on wound healing\textsuperscript{[33]}. Kiecolt-Glaser et al\textsuperscript{[39]} were among the first to carry out a qualitative study to investigate the consequence of long-term psychological stress caused by caring for a relative with dementia on wound healing. Participants included 13 healthy female carers and 13 controls. The subjects were inflicted with a 3.5 mm punch biopsy wound on the forearm. Hydrogen peroxide foaming and photography were used to assess wound healing. Complete healing was indicated by the absence of foaming upon application of hydrogen peroxide. The Perceived Stress Scale (PSS)\textsuperscript{[33]} was used to measure the degree to which situations in one’s life are appraised as stressful. Kiecolt-Glaser et al reported higher stress levels among carers and a delay in wound healing by an average of nine days compared with the control group.

In a similar study by Marucha et al\textsuperscript{[40]}, the impact of short naturalistic stressors on the healing rate of hard palate punched wounds was examined. Participants included 11 dental students inflicted with punch wounds where the first wound was induced during the summer holiday and the second was given three days before taking exams. Daily assessments of the wounds using hydrogen peroxide foaming and photography were conducted. Complete healing was reported there was no foaming at the biopsy site. At the time of each wounding, psychological stress was assessed using PSS\textsuperscript{[33]} and blood samples were collected to screen for the level of IL-1 in the blood.

The study revealed a delay in the wound healing rate and a decrease in IL-1 in the blood collected during the examination period compared with the results collected during the summer vacation. While both studies provided statistically significant results, the number of researchers and their experience in assessing wound healing was not clarified in the methodology\textsuperscript{[41]}. Moreover, both used hydrogen peroxide to evaluate wound healing and this may have given false results since hydrogen peroxide has the ability to damage non-epithelialised tissue and delay wound healing\textsuperscript{[41]}. Furthermore, negative health behaviour such as smoking\textsuperscript{[42]}, alcohol consumption, altered sleeping pattern\textsuperscript{[41]}, and nutrition\textsuperscript{[41]} are further putative factors caused by psychological stress that were not considered and might have contributed to the wound healing delay\textsuperscript{[41]}. Finally, the lack of accuracy of surface photography to evaluate deep tissue healing process compared with high resolution ultrasound\textsuperscript{[41]} and the small population used in both studies might throw doubt on the results\textsuperscript{[41]}.

A similar prospective longitudinal study was conducted by Ebrecht et al\textsuperscript{[43]}. The authors investigated the relationship between perceived stress and cutaneous wound healing in 24 healthy non-smoking males. Each participant was inflicted with
a 4 mm punch biopsy wound on the dominant arm and examined by high-resolution ultrasound scanning to assess healing progress at day 7, 14 and 21 post biopsy. Ebrecht and his team assessed perceived stress and health behaviour using both PSS[3] and the General Health Questionnaire[4]. Assessment of cortisol levels was conducted using saliva collected upon waking, two weeks before and two weeks after inflictng the wounds. The results demonstrated negative correlations between wound healing speed and both perceived stress and an increase in cortisol level, while a positive relationship was found between wound healing speed and optimism.

In contrast to the previous studies, Ebrecht et al[5] attempted to control imputed variables such as negative health behaviour that might have a direct impact on elevating stress level[6]. They also limited their recruitment to men to minimise the possibility of cortisol level difference between male and female participants[7]. Finally they used high-resolution ultrasound scanning to accurately assess healing activity in deep tissue wounds[8]. Despite the relevant result, the small sample size, young age and low comorbidity of the subjects, and short-term monitoring of the negative health behaviour might have an impact on the validity of the findings and the ability to generalise the outcome[9].

Studies have showed that patients experiencing psychological stress due to the presence of a chronic wound might develop depression[10]. Depression caused by psychological stress has an indirect impact on the delay in wound healing processes by affecting the patient’s behaviour and quality of life[10].

Cole-King and Harding[11] were among the first to examine the inter-relationship between depression and chronic wound healing in 53 males and females with chronic leg ulcers. A five point Likert scale[12] was used to rate wound healing and the Hospital Anxiety and Depression Scale (HADS)[13] was used to measure depression and anxiety. Wound and psychological assessments were measured with both researcher and participants blinded to the results of other procedures. Cole-King and Harding[11] reported a statistically significant result showing a direct relation between higher HADS scores and a delay in ulcer healing.

Despite the complexity in studying chronic wounds, Cole-King and Harding used relatively large size samples compared with similar studies and they also used validated psychological and wound assessment methods. They also managed to find a statistically significant relationship between psychological factors and wound healing. Nevertheless, physical complications and limitations[14], circulatory, hormonal and immunity alterations due to venous disease and diabetes[15] are factors that might have been relevant to the delay in healing that were not considered in this study.

Clinical relevance
Although the multidisciplinary team approach became a common practice in managing DFU, more attention is still given to the pathophysiology of disease[16]. The negative impact of psychological stress on wound healing that has been demonstrated in the studies discussed should urge the practitioners to give equal attention to the physiological and psychological aspects of wound healing when considering treatment plans[17]. The statistically significant results of psychological stress assessment tools like PSS[18] could be used in clinical practice to evaluate the psychological status of patients with DFUs, and to determine the scope of support to reduce their stress.

Early detection of patients’ perception, concern and reaction to their disease means that practitioners could provide effective management to prevent and treat DFU and minimise stress[19].

Conclusion
The worldwide incidence of DFU and its complications is increasing despite the improvement in prevention and treatment strategies[20]. Practitioners tend to give less focus to psychological stress within their management protocols. The past decade has witnessed a significant increase in research indicating the negative impact of psychological stress on wound healing. Studies have recruited healthy and health-compromised individuals to understand the mechanism of stress in slowing the healing rate of acute and chronic wounds using different stress and wound assessment tools. Concordant findings from these studies have revealed a direct correlation between psychological stress and alteration in glucocorticoid, catecholamine levels and cytokines function. A continuous increase in cortisol and catecholamine levels can have an

“Cole-King and Harding were among the first to examine the inter-relationship between depression and chronic wound healing in 53 males and females with chronic leg ulcers.”
impact on the immune and cellular response, downgrading pro-inflammatory cytokines and increasing blood glucose level, which would impair wound healing.

With the increased understanding of the significance of stress in wound healing, more research is required to study the correlation between psychological stress and wound healing in chronic wounds and DFU.

34. Sandholzer M. Combining qualitative and quantitative sampling, data collection, and analysis techniques in mixed-method studies. Nurs Res Health 2000; 23(3): 246–53