

Psychological Factors and Delayed Healing in Chronic Wounds

ALYS COLE-KING, MB BCH, DGM, MRCPsych, AND KEITH GORDON HARDING, MD, MRCCGP, FRCS

Objective: Studies have shown that stress can delay the healing of experimental punch biopsy wounds. This study examined the relationship between the healing of natural wounds and anxiety and depression. **Methods:** Fifty-three subjects (31 women and 22 men) were studied. Wound healing was rated using a five-point Likert scale. Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HAD), a well-validated psychometric questionnaire. Psychological and clinical wound assessments were each conducted with raters and subjects blinded to the results of the other assessment. **Results:** Delayed healing was associated with a higher mean HAD score ($p = .0348$). Higher HAD anxiety and depression scores (indicating "caseness") were also associated with delayed healing ($p = .0476$ and $p = .0311$, respectively). Patients scoring in the top 50% of total HAD scores were four times more likely to have delayed healing than those scoring in the bottom 50% (confidence interval = 1.06–15.08). **Conclusions:** The relationship between healing of chronic wounds and anxiety and depression as measured by the HAD was statistically significant. Further research in the form of a longitudinal study and/or an interventional study is proposed. **Key words:** delayed wound healing, depression, anxiety.

CI = confidence interval; HAD = Hospital Anxiety and Depression Scale; IL = interleukin.

INTRODUCTION

The epidemiology of wounds is extremely important, and both the social and personal costs need to be evaluated (1). Ruckley (2) points out that leg ulcers are "common, disabling, resistant to treatment, and expensive to manage." Leg ulcers of all etiologies affect an estimated 400,000 people in the United Kingdom, and it is thought that at any time about 25% are open and require treatment (3). The direct costs of treating various ulcers in the United Kingdom have been estimated at between \$218 and \$943 million annually (4). Any factors, including psychological factors, that influence healing could therefore have important cost implications.

The cellular processes of healing have been described by a number of authors (5). Tissue damage triggers a number of processes and activates various cells and cellular elements to achieve the complex events resulting in tissue restoration. The process of healing is orchestrated by a number of active tissue factors called cytokines, which are secreted by lymphocytes, platelets, and macrophages within the wound area. The tissue damage itself acts as a trigger for wound healing to begin.

Initially a normal clotting mechanism is required to activate succeeding stages. An inflammatory phase follows, which results in neutrophils, monocytes, and

macrophages appearing in large numbers in the wound area. Tissue macrophages play a major role in debridement of the area and secretion of peptides that stimulate neovascularization and the migration of lymphocytes and fibroblasts into the wound. Proliferation then occurs with the formation of collagen from the fibroblasts present in the wound area. The collagen matures, being remodeled and cross-linked, enhancing the tensile strength of the forming scar.

The cellular immune system seems to play the largest role in the regulation of these various phases of wound healing. Macrophages and T lymphocytes have the greatest influence on wound healing (6). IL-1 and tumor necrosis factor are the main chemokines released by these activated macrophages (7). T lymphocytes also participate in wound healing, migrating into the wounds after the inflammatory phase (8).

Normal wound healing is an extremely complex sequence of events that is affected by many things. No doubt good immune functioning is extremely important in regulating wound healing as well as in preventing wound infection, which can have a detrimental effect on normal healing. Although the cascade of events outlined above is seen in normal healing, one or more of the above processes may be compromised in some patients, resulting in delayed healing and formation of a chronic wound.

Psychoneuroimmunology has established a link between psychological factors and the endocrine and immune systems (9), and the role of the endocrine and immune systems in healing has been well researched (6). It is therefore possible that psychological factors have a role in the pathogenesis and recurrence of some chronic wounds (10, 11). Stotts and Wipke-Tevis (12) refer to research showing how psychophysiological stress has been identified as a cause of delayed healing. Palmer (13) discusses how psychological and psychosocial problems can affect wound healing, suggesting that the "psycho-social aspect of community

From the Wound Healing Research Centre, University of Wales College of Medicine, Cardiff, Wales, UK.

Address reprint requests to: Alys Cole-King, MB BCh, DGM, MRCPsych, Pwll Glas Resource Centre, Pwll Glas Road, MOLD, Flintshire, CH7 1RA, Wales, UK.

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nursing is often the most vital part of dealing with wounds that will not heal.”

Kiecolt-Glaser et al. (14) found that the healing of punch biopsy wounds “took significantly longer” in patients with dementia and that the caregivers of these patients reported significantly more stress than caregivers of control subjects. Examination stress was associated with delayed healing of hard-palate punch biopsy wounds in 11 dental students (15). The stress experienced by these subjects predated their punch biopsies and hence the delayed healing, suggesting a directional relationship between stress and delayed healing. The authors suggest that stress-related alterations in immune function may have impaired healing. Psychosocial stressors are known to contribute to some episodes of anxiety and depression; however, in these two studies general stress, rather than clinically significant anxiety or depression, was measured. Similar biochemical and endocrine changes can occur in both patients experiencing stress and those experiencing anxiety or depression.

Franks et al. (16) found a statistically significant mean reduction in depression in patients whose leg ulcers had healed, although the mean reduction in anxiety was not significant. However, these results must be interpreted with caution because they are based on the use of a psychological questionnaire, the Symptom Rating Test, that was not used for its intended purpose. The current study was designed to investigate the relationship between wound healing and clinically significant depression and anxiety as measured by a well-validated questionnaire.

METHODS

Consecutive patients attending the Wound Healing Research Unit for up to 3 months before entry into the study were invited to participate. Patients were referred by general practitioners within the former counties of South, Mid, and West Glamorgan and on a tertiary referral basis by hospital consultants. The 3-month maximum was chosen to reduce any bias that may have occurred by including patients receiving longer-term care. Long-term patients at this type of clinic would have wounds that were already known to be extremely difficult to heal.

Patients were required to give informed consent before entry into the study. At entry each patient's wound was assessed by a clinician and defined as being acute or chronic according to its underlying etiology. The HAD Scale (17) was administered to patients, who were blind to their rate of healing. Patients completed the questionnaires at home and returned them by post.

The HAD Scale was developed using data derived from outpatients between the ages of 16 and 65 years attending general medical clinics. Its authors suggest that the instrument would be valid in other hospital clinics, although they suggest that more work be done to validate this scale in the over-65 age group. The HAD Scale was designed to detect the psychic symptoms of a mood disorder and thus avoid symptoms that would be caused or affected by a physical illness.

The seven items of the depression subscale are based on one of the core features of a depressive illness, namely anhedonia. The items in the depression subscale have correlations ranging from +0.60 to +0.30, all significant beyond $p < .02$. The seven items chosen for the anxiety subscale were chosen from item analysis and revision of the Hamilton Anxiety Scale, and their correlations range from +0.76 to +0.41, with a significance level of $p < .01$. To test the reliability of the two subscales, HAD scores were correlated with scores on a clinical interview. HAD depression scores were compared with the severity of depression at interview, and a Spearman correlation of $r = 0.70$ was achieved. HAD anxiety scores were compared with the severity of anxiety at interview, and a Spearman correlation of $r = +0.74$ was achieved. Both correlations are statistically significant ($p < .001$).

The time period to which the HAD Scale refers was carefully chosen to eliminate overestimation of anxiety, particularly anxiety due to attendance at an outpatient clinic. This bias was further reduced by allowing patients to complete their questionnaires at home. The scale was devised to measure how patients had felt during the previous week.

HAD scores are presented in ranges that indicate the “probable absence,” “possible presence,” and “probable presence” of clinically meaningful degrees of the mood disorder. When the HAD Scale is used in research, the cutoff point for a case may be either the upper or lower end of the borderline range. In this study, a cutoff score of 9 was used for both subscales. The authors of the HAD suggest that patients who score above this cutoff will have a “possibility” of suffering from anxiety or depression so that there is a low proportion of false-negative results (17).

The rate of wound healing was assessed by the clinician in charge of the clinic, who was blind to the scores on the psychometric test. Previous research has shown that healing of some types of wound can be predicted (18). This clinical skill was combined with serial acetate wound tracings to evaluate the healing rate of the wounds. Acetate tracings are considered the most accurate measure of actual wound area (19). Approximately 3 months after entry into the study, the wounds were assessed for healing. No standard clinical method of measuring healing in all types of wound exists, so a five-point Likert scale was devised. The rate of healing of each wound was assigned a score of 1 to 5, where 1 was “healing well” and 5 was “not healing.”

At the same time the presence of any clinical infection in the wound was determined by clinical features (20).

The results were analyzed with SPSS software, using χ^2 , analysis of variance, and the Mann-Whitney test. A significance level of 5% was accepted, and a one-tailed test was used.

RESULTS

This article presents only the results of patients with chronic wounds of the lower leg. The type of wound was limited to avoid any bias that could result from analyzing both acute and chronic wounds, because the etiology of such wounds and the demographic characteristics of patients would be so different. These chronic leg ulcers were due to venous disease either in isolation or in combination with ischemic disease. Fifty-nine patients with chronic leg ulcers were initially recruited into the study. Of these, 53 patients, 31 women (58.5%) and 22 men (41.5%), completed and returned the questionnaires (a 90% response rate). No association was found between failure

to return a questionnaire and sex, presence of infection in the wound, or delayed wound healing (note that all 59 patients' wounds were assessed). Failure to return the questionnaire was therefore assumed not to be a source of bias. The demographic characteristics of the patients are detailed in Table 1.

Wound healing rates were compared with the psychometric test scores. This comparison was done using both the original psychometric score and a cutoff score of 9. When the cutoff score was used, patients who scored 9 or above were considered to have a disorder (ie, a case of depression or anxiety). This cutoff was chosen because it provides a low proportion of false-negative results. For the analysis of wound healing, patients were divided into two groups: patients who were healing well (healing well or moderately; ie, scores of 1 or 2) and those who had delayed healing (healing slowly, healing very slowly, and not healing; ie, scores of 3, 4, or 5).

Sixteen patients scored as HAD anxiety cases, and 15 of them had delayed healing (using the Fisher exact test, $p = .02625$). HAD anxiety cases were 8.12 times more likely than noncases to have delayed healing (95% CI = 0.96–68.63), although this value must be interpreted with caution because the lower value is <1.0. Thirteen patients scored as HAD depression cases, and all of these had delayed healing (Fisher exact test: $p = .00965$). There were no significant differences in anxiety and depression scores between the three categories of nonhealers. Table 2 shows the relationship between HAD "caseness" and healing scores.

Using actual psychometric scores, patients scoring in the top 50% of HAD scores were more likely to be in the delayed healing group (Mann-Whitney test: $Z = -2.4286$, $p = .0152$). In fact, they were four times more likely to be in the delayed healing group than those scoring in the bottom 50% (95% CI = 1.06–15.080). The relationship between HAD caseness and wound healing seems to be additive and is shown in Table 3.

TABLE 1. Age, Sex, and Infection Rates of Subjects According to Healing Rate

Healing Rate ^a	Subjects (N)	Age (y)		Sex				Infection	
		Mean	Range	Male		Female		N	%
				N	%	N	%		
Well (1)	2	61	48–74	2	100	0	0	0	0
Moderately (2)	12	68	38–87	4	33	8	67	2	17
Slowly (3)	14	63	22–82	7	50	7	50	3	21
Very slowly (4)	16	66	31–91	6	38	10	62	12	75
Not healing (5)	9	68	59–81	3	33	6	67	7	79

^a Healing score, based on a five-point Likert scale.

TABLE 2. HAD Anxiety and Depression and Wound Healing Scores

Healing Score	HAD Anxiety Cases ^a		HAD Anxiety Depression Cases ^b	
	N	%	N	%
1	0		0	
2	1	6	0	
3	5	31	4	31
4	6	37	6	42
5	4	25	3	23

^a Mann-Whitney test: $Z = 1.9806$, $p = 0.0476$.

^b Mann-Whitney test: $Z = 2.1560$, $p = .0311$.

TABLE 3. Healing Groups and HAD Caseness^a

Healing Group	Noncase		Depression or Anxiety		Depression and Anxiety	
	N	%	N	%	N	%
Healing	13	40	1	8	0	
Delayed healing	19	60	12	92	8	100

^a ² test: Pearson $r = 8.54049$, $df = 2$, $p = 0.01398$.

DISCUSSION

These results show that there is a statistically significant relationship between psychological factors and wound healing. If anxiety and depression do cause delayed wound healing, several mechanisms can be suggested. Psychological factors could act both directly or indirectly. Psychological factors can disrupt the activity of macrophages and lymphocytes in the healing process. Depression is associated with widespread impairment of both cellular and humoral immunity (21). Research has shown that stress can influence the secretion of proinflammatory cytokines at an actual wound site, and this is a possible mechanism by which stress may delay wound healing (22).

Indirect factors that might lead to delayed healing in a depressed individual include self-neglect, disturbed sleep, and poor appetite. Poor sleep may reduce the production of an anabolic endocrine environment and thus delay wound healing (23). The sleep disturbances of depression and anxiety are well established, particularly in depression. Sleep deprivation can interfere with the immune system, disrupting the crucial role of macrophages and lymphocytes (24, 25).

The secretion of chemokines released by activated macrophages (eg, IL-1 and IL-2) may be related to the sleep-wake cycle (26, 27). As mentioned earlier, IL-1 is

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particularly important for normal wound healing (6). Poor appetite leading to malnutrition, specifically vitamin and trace element deficiencies, could interfere with healing. Wound infections interfere with healing, and psychological factors acting on the immune system might make a patient more susceptible to infection.

This study is cross-sectional in design and therefore does not demonstrate a causal relationship. Its robustness would have been enhanced if wound healing had been independently rated by two surgeons, but it was designed to be a pilot study to investigate whether a relationship between anxiety and depression and healing might exist. It is important to note, however, that in addition to the subjective clinical skill used to assess the wounds (18), an objective method, acetate wound tracings, was also used to assess the rate of healing.

The authors of the HAD Scale have suggested that more work is needed to validate the use of this scale in the over-65 age group. Although such work was not done in this study, there was no relationship between age and HAD scores, suggesting that age was not a cause of bias in this study.

The results of this study are insufficient to explain the mechanism for the observed relationship. However, if a causal relationship does exist, it seems likely that delayed healing is a result of psychological factors rather than the reverse. This proposal is supported by other research (14, 15, 22).

To the best of our knowledge, this is the first study to examine the rate of healing of chronic leg ulcers and its relationship to anxiety and depression, which were assessed using a well-validated psychometric instrument. The study provides additional evidence supporting a relationship between psychological factors and wound healing. The results are particularly meaningful because the study was conducted in an outpatient clinic rather than an experimental environment. In addition, the methodology used in this study could be used in routine clinical practice. Some of the previous studies, despite having interesting results, have used small samples; consequently, the results did not show statistically significant differences. Also, almost none were specifically designed to investigate the relationship between wound healing and anxiety and depression.

We suggest that further research be conducted to clarify the relationship between healing and clinically significant anxiety and depression. It would be worthwhile to fully validate the Likert scale used to determine the rate of healing, particularly for different types of wounds. In addition, work might be done to operationalize the different categories of healing so that higher interrater reliability could be achieved. A prospective, randomized interventional study would be

worthwhile to evaluate the effect of psychiatric treatment on healing rates in patients with chronic wounds who are experiencing clinically significant anxiety or depression.

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William Greene, MD, a past President of APS — 1967–68