

Psychological stress and wound healing

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SUMMARY: Stress and different mental states have a significant effect on the progress of wound healing. It has been shown that stress can change the production of cytokines and thus interfere with the healing process. Interesting studies with animals, stressed students, married couples, Alzheimer caregivers, depressed, anxious individuals, people with anger issues and other uncover a significant influence that stress has on the progress of wound healing. Wounds created with punch biopsy, tape stripping and blister wounds are often used to measure this influence. The importance of intervention methods used for decreasing stress and its impact are discussed.

KEYWORDS: Stress, Wound healing, Psychoneuroimmunology, Cytokines

Over the years as the field of psychoneuroimmunology progressed, it became evident that experiences of stress and stress related emotional states can affect the immune system. Developing connections between mental states and health provided a clear practical value for the treatment of diseases and injuries. The contribution of this data can be seen when examining the effect stress and different mental states have on the progress of wound healing. Disruptions in the wound healing process can prolong hospital stay, create greater discomfort for the patient, increase the risk for wound infections and delay the return of the patient to regular life activities .

Stress can interfere with the immune system. To be more precise, it can restrain the production of proinflammatory cytokines and chemokines, such as interleukin (IL)-1 α , IL-1 β , IL-8, IL-6, IL-2, and transforming growth factor β (TGF- β), vascular endothelial growth factor, tumor necrosis factor α (TNF- α) . Consequently, the stages of the wound healing process are disrupted. Wound healing progresses through several overlapping stages and any delay in any one of these stages can slow down the complete phase of the wound healing process. This is especially true for the first stage since the success of later phases is immensely dependent on previous phases. The factors mentioned above act as attractants for the migration of other cells to the site. Thus starts the second phase that involves the recruitment and replication of cells that are needed for tissue regeneration and capillary regrowth. Finally, the third step, wound remodeling, can continue for weeks or months.

Measuring stress

There are many definitions of stress. Cöhler, Kessler and Gordon point out that they vary in the way they evaluate stressful events, responses or individual appraisals of situations as the central characteristics of stress. Stress is commonly described as a state in which events or environmental demands go beyond an individual's perceived ability to cope. When assessing the influence that stress can produce, there are three main approaches. The environmental approach focuses on assessment

of environmental events and experiences that are objectively associated with substantial adaptive requirements. This can include giving participants a check list of stressful life events. The psychological approach focuses on individuals subjective evaluations of their abilities to cope with the demands posed by specific events or experiences. Instead of just listing events, a subject can evaluate how much he felt overwhelmed by them. The biological approach focuses on activation of specific physiological systems that have, in lot of studies, been shown to be modulated by demanding conditions. For instance, this can include measuring cortisol levels.

Analysis of any immune parameter should be viewed in the context of other parameters. It is generally assumed that suppressed immune indicators represent impaired immune function. Even so, increased levels of an immune indicator are not necessarily a result of a competent immune response. Heightened immune parameters may imply that the immune system is dysregulated which can lead to injurious to health

Health related behaviors

Besides measuring stress levels, in this line of research it is of major importance to track a number of health related behaviors such as sleep, alcohol intake, caffeine intake or exercise. This is because when under a lot of stress people often change their behavior. A student will probably drink more coffee and exercise less when taking exams. Or people might use more alcohol or smoke more when they are under emotional stress. This might slow the wound healing process, but cannot be attributed to the sole effect of a stressful state.

Creating wounds and measuring healing

The most compelling evidence of the effect stress has on wound repair is provided by studies in which standard wounds are created experimentally and researchers monitor the healing process. The healing of the wound is measured by extracting and examining fluid from the wound or by measuring the time





Fig 1. Punch biopsy tools

it took for the wound to heal. The latter can be done by taking pictures of the wound and measuring the changes objectively. Experimentally made wounds are a great tool for measuring the body's immune reactions, since, as we mentioned, measuring immune parameters alone, could be tricky to interpret.

There are three methods of creating small wounds that are used to study the effect of stress on wound healing. One of the methods, often used, is tape stripping. Participants may be subjected to repeated application of cellophane tape to remove a layer of epidermis cells. This causes a disruption of the stratum corneum barrier function of the skin. The procedure affects epidermal permeability. Wound healing is then assessed by measuring the rate of recovery of the skin barrier using Transepidermal Water Loss measurements. Damage to the stratum corneum and superficial skin layers not only results in physical vulnerability, but also results in an excess rate of water loss that is observed. Another method of creating a wound commonly used in this kind of research is punch biopsy. Punch biopsies can be used to inflict standard full thickness dermal wounds as well as mucosal wounds. This is a low risk technique which provides very similar wounds between participants. Wounds are usually between 1.5 and 4 mm deep. Healing is examined with daily pictures of the wound or in some cases with daily response to hydrogen peroxide. They provide the material to quantify the changes in wound size over time. Wound healing can also be assessed using more advanced techniques such as ultrasound biomicroscopy. Finally, there are experiments which consist of creating blister wounds and measuring their healing process. The wound is created by using a vacuum pump on the forearm. This pump creates a separation of the epidermis from the dermis. The created suction is gentle and takes about an hour to create a wound. With this method, data on cytokine production can be collected at the wound site. During this method wound healing is also observed by measuring transepidermal water loss. Water loss is measured by the use of a Computerised evaporimetry instrument, such instruments measure the vapor pressure gradient above the surface of the skin.

Studies done

Garg, Chren, Sands, Matsui, Marenus, Feingold and Elias carried out a research on twenty-seven medical, dental and pharmacy students. Students were subjected to tape stripping on three occasions: after their winter vacations, after their spring vacations and during their final examination week. During the examination period skin barrier healing was notably prolonged at 3, 6 and 24 hours after the tape stripping procedure compared with the winter and summer vacation periods. Students who reported experiencing less stress during the examination period had faster recovery in skin barrier function than those who reported that they were under more stress. In another research using punch biopsy, 11 dental students underwent this procedure during their summer vacation and again three days before a major exam. Mucosal wounds were created on their hard palate. Wounds inflicted before exams healed on average 3 days longer (40% longer) than those made during summer vacation. What is even more remarkable, no student healed as fast throughout the duration of exam period as during the vacation. Decrease in IL-1 β mRNA levels was found in stimulated peripheral blood leukocytes of students under stress. In a similar study using punch biopsy, it was calculated that the correlation between perceived stress and wound healing was -0.59.

It seems that a common stressor such as taking an exam can have a significant influence on wound healing. Comparable to such stress, undergoing an interview in an experimental setting has also been shown to prolong wound healing. A research involving tape stripping technique was conducted on 25 healthy women. After a task where they had to talk about why they are the best candidates for a job and answer additional questions from interweavers, there was an increase in their plasma cortisol, norepinephrine, IN-1, IN-10, TNF-levels. Also, there was an increase in circulating natural killer cell activity and natural killer cell number.

Another sizeable source of stress can be encountered by some married couples. A troubled marriage with hostile marital interactions can affect body's immune response. Despite the fact that considerable early local production of proinflammatory cytokines helps with enhanced healing, greater systematic creation of proinflammatory cytokines can indicate a maladapted response. In this crossover trial, forty-two couples went to a hospital unit for research purposes lasting 24 hours. During the first stay they had a social support interaction and on the second visit they had to talk about a disagreement in their marriage that troubled them. Before interactions they were administered eight small 8mm blister wounds. Besides wound healing and changes

in proinflammatory cytokine production, couples interpersonal behavior and other characteristics were assessed. Wounds healed more slowly following the disagreement interaction than after the social support interaction. Subsequently, local cytokine production of IL-1 β , IL-6 and TNF- α was lower at the wound site in the same comparison. It is interesting that couples that were classified as hostile healed 60% slower than low-hostile.

Taking care of an ill relative is another recurrent source of stress. Kiecolt-Glaser, Marucha, Malarkey and Glaser investigated the effects of stress caused by taking care of a relative with Alzheimer's disease on wound healing. A punch biopsy wound was administered to 13 women caregivers, as well as to 13 women of the control group matched for age and income. Wound healing process took on average 9 days longer (24% longer) in caregivers than in the control group women. Periphetal-blood leukocytes from caregivers created significantly less interleukin 1 β mRNA after lipopolysaccharide stimulation than did controls cells.

How to put this knowledge to good use?

In one study, in an experimental setting, individual writing sessions of 20 minutes were scheduled for 36 participants over three consecutive days. Two weeks after the first session they received a punch biopsy wound. The experimental group was instructed to write about a traumatic and upsetting event in their life with the advice to dwell deep in their emotions. The control group was instructed to write about time management. This low cost and brief intervention showed that participants

who wrote about traumatic experiences had significantly smaller wounds 14 and 21 days after the biopsy compared to those who wrote about time management.

These studies have shown that stress can delay the healing of an experimentally created wound. Another study looked into the influence of naturally stressful emotional conditions such as anxiety and conditions like depression, which can also impact the inflammatory system and wound healing. Delayed healing of a punch biopsy wound was correlated with a higher score on the Hospital Anxiety and Depression Scale. Patients that were in the top 50% of total HAD scores, were four times more likely to experience delayed healing than the other half.

This indicates the possibility of using interventions or even medication to relive negative emotional states and stress for securing better wound healing and overall recovery after injuries or surgeries. Results in a study conducted on animals, using fluoxetine, show that pharmacological stress reduction can also improve wound healing. Also, it has been shown that serotonin-specific reuptake inhibitors (SSRIs) can incite the progress of inflammation. They can inflect the interleukin and interferon production. Hence, SSRIs therapy could also be considered as a possible wound healing treatment.

Social support has also been shown to quicken the healing process. The punch biopsy wounds healed slower in mice that were housed alone than mice which were living in pairs. Interventions on humans that have generally produced positive endocrine and immune changes include cognitive behavioral interventions, exercise, relaxation, classical conditioning and self-disclosure. Relaxation techniques can include progressive muscle relaxation, focused breathing, guided imagery and visualization, meditation techniques, massage, lying quietly with closed eyes, saying "so" and "hum" on inhalation and exhalation, biofeedback, hypnosis, hypnosis with immune altering suggestion or just watching a funny movie.

Other specific interventions, such as those used to help people manage anger, could also be beneficial for wound healing. In a study examining certain patterns of anger expression, the anger control variable predicted wound healing better than it could be predicted by variability in hostility, negative affections, social support and health behaviors. In addition, subjects who were less able to control anger showed higher cortisol reactivity during the administration of a blister wound. The increased cortisol levels were in turn related to longer healing time.



Fig 2. Study stress



Fig 3. Relaxing

Conclusion

Stress does significantly impair wound healing. It has also been showed that psychological intervention decrease stress. It was William James who once stated: “The greatest weapon against stress is our ability to choose one thought over another”. Having that in mind, it is sufficient to say that psychological interventions should be more frequently incorporated into the health care system in view of the fact that they can enhance the wound

healing process, preserve mental well-being and lower the overall cost of long hospital stays.

Future studies should concentrate on discovering which of these techniques are most efficient and practical in the case of boosting the wound healing process. This should be done by taking into account individual differences, since not every intervention can be considered equally appealing to everyone.

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Psihološki stres i zarastanje rana

SAŽETAK: Stres i različita mentalna stanja imaju značajan učinak na zarastanje rana. Pokazano je da stres može utjecati na produkciju citokina i tako djelovati na proces zarastanja. Zanimljiva istraživanja sa životinjama, studentima pod stresom, bračnim parovima, osobama koje se brinu o bližnjima oboljelim od Alzheimerove bolesti, depresivnim, anksioznim i osobama sa problemima sa ljutnjom otkrivaju utjecaj stresa na tijek zarastanja rana. Za mjerenje tog utjecaja često se koristi punch biopsija, opetovana primjena ljepljive trake na koži i namjerno stvoreni plikovi. Naglašava se i važnost primjene tehnika intervencija za smanjivanje stresa i boljeg zarastanja rana.

KLJUČNE RIJEČI: Stres, Zarastanje rana, Psihoneuroimunologija, Citokini