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Omega-3 Fatty Acids and Stress-Induced Immune Dysregulation: Implications for Wound Healing

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Abstract

Stress-related immune alterations can be consequential for health; they can enhance susceptibility to infectious agents and influence the severity of infectious disease, diminish the strength of immune responses to vaccines, reactivate latent viruses, and slow wound healing. Furthermore, stressful events and negative emotions promote systemic proinflammatory cytokine production while reducing beneficial local production of proinflammatory cytokines at the wound site that are important for wound healing. Dietary omega-3 and omega-6 polyunsaturated fatty acids (PUFA) also influence systemic inflammation; high proportions of omega-6 to omega-3 boost inflammation, while omega-3 has anti-inflammatory properties. Additionally, the limited evidence thus far suggests that omega-3 PUFA may enhance local inflammatory responses at wound sites. Moreover, an individual's dietary proportion of omega-3 to omega-6 may influence the magnitude of inflammatory responses to stressful events. Thus, wound healing and surgery provide exemplars of how stress and depression can interact with the diet to influence important clinical outcomes.

Keywords

Psychoneuroimmunology; Interleukin-6 (IL-6); C-reactive protein; Proinflammatory Cytokines; Depression

INTRODUCTION

Stressful events and negative emotions can have clinically significant consequences for many aspects of the immune response, including inflammation, which is the focus of this paper. Dietary omega-3 and omega-6 polyunsaturated fatty acids (PUFA) also influence

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inflammation, and may also modulate the magnitude of inflammatory responses to stressful events. After addressing behavioral and dietary influences on inflammation, we discuss their contributions to wound healing and surgery, providing one example of how stress and depression can interact with the diet to influence important clinical outcomes.

DISCUSSION

Stress, depression, and inflammation

The central nervous system (CNS), the endocrine system, and the immune system interact with each other, and a variety of stressors ranging from academic examinations to marital conflict to caregiving for an impaired family member can dysregulate the immune response by affecting the interplay of these systems. These stress-related immune alterations can be consequential for health; they can also enhance susceptibility to infectious agents and influence the severity of infectious disease, diminish the strength of immune responses to vaccines, reactivate latent herpesviruses, and slow wound healing[1]. Moreover, negative events and negative emotions can also substantially enhance inflammation, a primary focus for this paper.

Psychological stress is frequently a precursor to the onset of depressive symptoms, and inflammatory pathways are implicated in this link. Although conceptually distinct, both stress and depression involve negative mood, activation of the nervous and endocrine systems, and associated negative health outcomes [2]. Moreover, the experience of long term depression can itself be conceptualized as a chronic stressor. For these reasons, studies focusing on depressive symptoms and inflammation are highly relevant to gaining a full understanding of the effects of stress.

Inflammation is a crucial, fundamental response to infection and injury; proinflammatory cytokines including interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-α) attract immune cells to the site of infection or injury, and prime them to become activated to respond. Although the mechanisms associated with inflammation are critical to resolving infections and repairing tissue damage, exaggerated responses and/or chronic inflammation can have negative health consequences including cardiovascular disease, type II diabetes, arthritis, osteoporosis, and periodontal disease[3, 4]. In addition, inflammation is now considered a risk factor for most cancers because of the evidence that proinflammatory cytokines influence tumor promotion, survival, proliferation, invasion, angiogenesis, and metastases[5].

Psychosocial stress and depression contribute to a greater risk for infection, prolonged infectious episodes, and delayed wound healing, all of which can fuel sustained proinflammatory cytokine production[1]. However, stress and depression can also directly provoke proinflammatory cytokine production in the absence of infection or injury[3, 6]. What is more, inflammation is implicated in the pathophysiology of depression; stressful events can clearly precipitate depression, perhaps in part because they also propel inflammation[7]. Additionally, there is evidence that both clinical depression and subsyndromal depressive symptoms may sensitize or prime the inflammatory response, thus effectively promoting larger cytokine increases in response to stressors as well as antigen challenge[8, 9].

Furthermore, depression and stress alter inflammation-relevant health behaviors; for example, disturbed sleep, a common response to negative emotions and emotional stress responses, promotes IL-6 production[10]. Accordingly, depression and stress can effectively modulate secretion of proinflammatory cytokines both directly and indirectly. Through these pathways, depression and stressful experiences contribute to both acute and chronic proinflammatory cytokine production[11, 12].

Diet and inflammation

Diet also influences the synthesis of proinflammatory cytokines. Arachidonic acid (AA) derived (omega-6) eicosanoids (primarily from refined vegetable oils such as corn, sunflower, and safflower) increase the production of proinflammatory cytokines IL-1, TNF-α, and IL-6, operating as precursors of the proinflammatory eicosanoids of the prostaglandin (PG)2-series[13, 14]. In contrast, the omega-3PUFA, found in fish, fish oil, walnuts, wheat germ, and some dietary supplements such as flax seed products, can curb the production of AA derived eicosanoids[13, 14]. Thus it is not surprising that both higher levels of omega-3 PUFA as well as lower proportions of omega-6 to omega-3 are associated with lower proinflammatory cytokine production[15].

The fatty acid composition of the modern Western diet has changed dramatically over the last century. In the US, it is estimated that the omega-3 to omega-6 ratio in the typical diet in 1999 was 9.6:1, representing an increase of between 42–77% from 1909[16]. This shift reflects fundamental changes in dietary patterns, including considerable increases in use of refined vegetable oils – a primary source of omega-6 – and relative reduction in consumption of fish, nuts, seeds and leafy green vegetables. In contrast, the ratio of omega-3 to omega-6 PUFAs in the early hunter-gatherer diet was 2:1 to 3:1[17]. The dramatic shift in omega-6 relative to omega-3 consumption in the modern diet is believed to contribute to increases in numerous inflammatory-related diseases,[18] including depression for which inflammatory pathways play a clear etiological role[7].

Relatedly, epidemiological studies have demonstrated significant inverse relationships between annual fish consumption and prevalence of major depression—the more fish eaten, the lower the prevalence of serious clinical depression[19]. A number of researchers have shown that depressed patients have, on average, lower levels of omenga-3 in their blood than nondepressed individuals; furthermore, they have found evidence that greater severity of depression is linked to lower levels of omega-3[20]. A number of well-controlled depression treatment studies have found therapeutic benefits following omega-3 supplementation[20]. Detailed below, the antiinflammatory effects of omega-3 PUFAs are a clear mechanistic pathway for these effects. Clearly, these key dietary pathways have implications for both psychological and immunological responses.

Mechanistically, transcription factor nuclear factor kappa B (NF-κB) activation is a prime pathway for upregulating proinflammatory cytokine production[21, 22]. Psychological stress promotes NF-κB activation, providing a channel for translating psychological stress into mononuclear cell activation[22]. In contrast, two key omega-3 PUFA, eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), can substantially decrease lipopolysaccharide-induced (LPS-induced) TNF-α expression by blocking NF-κB activation[21]. Thus, omega-3

PUFA may attenuate stress-related increases in inflammation through alterations in NF-κB activation, as well as through their positive effects on mood.

If the joint contributions of diet and behavior to inflammation were simply additive, they would certainly be important. However, as described below, an individual's dietary omega-3 or dietary proportion of omega-6 to omega-3 may influence the magnitude of inflammatory responses to depression and stressful events.

Omega-3 fatty acids and stress-related inflammatory changes

One provocative study addressed the question of whether the relative balance of omega-6 and omega-3 PUFA would predict a larger inflammatory response to stress. Medical students who had lower serum omega-3 or higher proportions of omega-6 to omega-3 demonstrated greater TNF-α and interferon-gamma (IFN-γ) production by LPS-stimulated peripheral blood leukocytes (PBLs) during exams than those with higher omega-3 or lower proportions[13].

Furthermore, another study with older adults suggested that depressive symptoms and the proportion of omega-6 to omega-3 worked together to enhance inflammation beyond the contribution provided by either variable alone [23]. Although predicted cytokine levels were fairly consistent across the proportions of omega-6 to omega-3 with low depressive symptoms, higher proportions of omega-6 to omega-3 were associated with progressively elevated TNF-α and IL-6 levels as depressive symptoms increased.

Together, these two studies with medical students and older adults[13, 23] suggest that an individual's dietary omega-3 or proportions of omega-6 to omega-3- may influence the magnitude of inflammatory responses to depression and stressful events. The evidence that behavioral and dietary vulnerabilities are not merely additive provides a window for considering new multidisciplinary prospects. Indeed, wound healing and surgery provide several possible exemplars of how stress and depression may interact with the diet to influence important clinical outcomes.

Stress and wound healing

Wound repair progresses through several overlapping stages[24]. In the initial inflammatory stage, vasoconstriction and blood coagulation are followed by platelet activation and the release of platelet-derived growth factors (PDGFs) as well as chemoattractant factors released by injured parenchymal cells. Cytokines and chemokines, such as IL-1α, IL-1β, transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), TNF-α, and IL-8 play important roles in the early stage of wound healing. These factors act as chemoattractants for the migration of phagocytes and other cells to the site, starting the proliferative phase which involves the recruitment and replication of cells necessary for tissue regeneration and capillary regrowth. The final step, wound remodeling, may continue for weeks or months. Thus, the healing process is a cascade and success in the later stages of wound repair is highly dependent on initial events[24].

Inflammation plays a key role early in this cascade, and proinflammatory cytokines are essential to this effort; they help to protect against infection and prepare injured tissue for

repair by enhancing the recruitment and activation of phagocytes[25]. Furthermore, cytokines released by recruited cells regulate the ability of fibroblasts and epithelial cells to remodel the damaged tissue[25]. IL-1 produced early after tissue injury can regulate the production, release, and activation of metalloproteinases that are important in the destruction and remodeling of the wound. IL-1 also regulates fibroblast chemotaxis and the production of collagen[25]. Moreover, IL-1 stimulates the production of other cytokines that are important for wound healing, including IL-2, IL-6, and IL-8[25]. Accordingly, deficits early in the wound repair cascade can have adverse consequences downstream.

Stress disrupts the production of proinflammatory cytokines that are important for wound healing, which is one mechanism that produces substantial delays in wound repair. In humans, a suction blister model provides a way to measure immune responses that are central to the early stages of wound healing *in vivo*, at the actual wound site, providing key data on the inflammatory response with direct clinical relevance[26, 27]. This model allows investigators to study the migration of neutrophils and macrophages and production of cytokines at wound sites for the first day or two after wounding. Commonly, after raising several blisters and removing their roofs (the epidermis), plastic templates with wells containing a salt solution and autologous serum are placed over the lesions, and cells migrate to the wound sites and collect in the wells. The serial collection of samples from the wells over time allows for cell phenotyping and cytokine measurement as the local immune response evolves. Using this approach to study stress and wound healing, women who reported more stress produced significantly lower levels of two proinflammatory cytokines important for the early stages of wound healing, IL-1α and IL-8[26].

Further work using this suction blister model showed that even a commonplace everyday stressor, a marital disagreement, could influence wound healing, as well as local and systemic proinflammatory cytokine production. To separate the effects of the acute stress of a marital conflict from the chronic strains of marital discord on local and systemic proinflammatory cytokine production as well as wound healing, couples were recruited for two 24-hour admissions to a hospital research unit[11]. On each admission a suction blister protocol provided a mechanism for studying the local inflammatory responses *in vivo*; healing at the blister sites was assessed daily following discharge. During the first admission, spouses had a structured social support interaction; during the second admission, couples discussed an area of disagreement.

Couples' blister wounds healed more slowly, and cytokine production (IL-1β, IL-6, and TNF-α) was lower at wound sites following marital conflicts than after social support interactions. Couples who were more hostile towards each other during both discussions healed wounds more slowly than couples whose interactions were less hostile. The overall differences related to hostility were substantial, for instance, small blister wounds in high hostile couples healed at only 60% of the rate in low hostile couples. Thus, wound healing appeared to be responsive to both the acute stress of a conflict, as well as hostile behaviors.

Although greater early local production of proinflammatory cytokines at wound sites is beneficial because it is associated with enhanced healing, greater systemic production of proinflammatory cytokines can represent a maladaptive response[1]. Compared to low hostile

behavior couples, high hostile couples had relatively greater increases in circulating levels of plasma IL-6 and TNF-α following a conflict discussion than a social support interaction. Indeed, low hostile participants produced roughly the same increment in IL-6 over 24 hours following either a social support or conflict interaction (65% vs. 70%), while IL-6 production for high hostile individuals jumped from 45% to 113%.

Other studies have demonstrated that stress can also delay healing of full-thickness dermal and oral wounds. For example, women who were experiencing the long-term stress of caregiving for a relative with Alzheimer's disease took 24% longer than well-matched controls to heal a small, standardized dermal wound[28]. In a population of dental students, mucosal wounds placed three days before a major examination healed an average of 40% more slowly than identical wounds made during summer vacation. Importantly, the differences among the group of 11 students were very consistent, no student healed as rapidly during examinations as during vacation[29].

Studies with mice have confirmed and extended the data obtained with humans. Mice subjected to restraint stress healed a standardized 3.5-mm full thickness cutaneous punch biopsy wound an average of 27% more slowly than control mice[30]. Analysis of the cellularity of wound sites using cross-sections of dermal and epidermal layers showed less leukocyte infiltration to the wound sites in restraint-stressed mice at one and three days after wounding, compared to controls[30]. Serum corticosterone levels in the restraint-stressed group were more than four times as large as those of the controls, a well-replicated endocrine stress response[30]. Blocking glucocorticoid receptors in restraint-stressed animals with RU40555 resulted in healing rates that were comparable to control animals[30]. Accordingly, these data provide evidence that disruption of neuroendocrine homeostasis modulates the early stages of wound healing.

Higher levels of glucocorticoids have a number of adverse effects on various components of the wound healing process; for example, they may slow wound healing by altering local levels of proinflammatory cytokines. Hübner et al.[24] showed that the strong and early induction of IL-1α, IL-1β, and TNF-α expression at the site after wounding was significantly reduced following pretreatment of mice with glucocorticoids. Similarly, human studies have demonstrated that stress-induced elevations in glucocorticoids can transiently suppress IL-1β, TNF-α, and PDGF production[31]. Accordingly, dysregulation of glucocorticoid secretion provides one obvious neuroendocrine pathway through which stress alters wound healing.

While slowing wound healing, stress also increases susceptibility to wound infections[32]. Compared to control mice, restraint stress delayed wound healing by 30% and facilitated a 2–5 log increase in opportunistic bacteria such as *Staphylococcus aureus*. By day 7 following wounding, 85.4% of restraint-stress mice had bacterial counts predictive of infection, compared to 27.4% of controls [32]. In accord with these data, other researchers have also found that stress impairs the skin's barrier function, resulting in increased severity of cutaneous infections in mice[33].

Thus, convergent data from mouse and human studies have demonstrated that stress has substantial adverse effects on wound repair, and also increases risk for infection. In agreement with these laboratory findings, several studies have shown that greater fear or distress prior to surgery is associated with poorer outcomes including longer hospital stays, more postoperative complications, and higher rates of rehospitalization[34].

Proinflammatory responses associated with wounding and surgery: role of omega-3 fatty acids

A novel randomized, double-blind, repeated measures trial using the suction blister model with omega-3 supplementation suggested that omega-3 fatty acids could have beneficial effects at the wound site[35]. Following four weeks of supplementation with either 2.7 g/day of omega-3 fatty acids or a mineral oil placebo, IL-1β, TNF-α, and IL-6 were measured in the blister wells of 30 healthy male and female volunteers ages 18–45 years using the suction blister model described earlier. Although all cytokines were higher in the omega-3 treatment group, only IL-1β was significantly elevated compared to the controls. These data provide supportive mechanistic information for several surgical studies highlighted below.

Surgery stimulates a general inflammatory response with characteristic increases in proinflammatory cytokines such as IL-6 and IL-1β, as well as compensatory anti-inflammatory responses including IL-10, IFN-γ, and IL-1 receptor antagonist[36]. Although this general inflammatory response is an important immune defense, excessive and/or prolonged inflammatory responses can provoke organ dysfunction and multi-organ failure[37]. Although the literature is limited, several provocative studies suggest that omega-3 PUFA supplementation is beneficial.

In abdominal surgery, complications following extended interventions include the systemic inflammatory response system (SIRS), which is a leading cause of postoperative fatalities[36]. In one study, 24 male and female patients ages 44–80 years scheduled for extended abdominal surgeries were randomized to receive 10g of fish oil (30–70% omega-3) beginning the day before surgery and continuing through postoperative days 1–5; the control group received the same infusion protocol without omega-3. The postoperative IL-6 response was significantly lower in the omega-3 treatment group compared to the controls, without group differences in TNF-α, CRP, white cell count, or neutrophil respiratory burst activity. Monocyte expression of human leukocyte antigen-BR, important for antigen presentation, declined in controls but remained stable in the fish oil group. Furthermore, the omega-3 group had a shorter hospital stay as well as lower rates of severe infection[36].

Another trial examined 60 men and women undergoing large bowel surgery for malignant or benign conditions. Patients were, on average, in their mid-60s. Each was randomized to receive either 1) lipid-3 total parenteral nutrition, or 2) parenteral nutrition including 10% soybean oil, or 3) 8.3% soybean oil +1.7% fish oil for 5 days postoperatively. The groups did not differ in terms of changes in cell numbers or mitogen-stimulated lymphocyte proliferation; however, fish oil benefited both stimulated IL-2 and IFN-γ production. Accordingly, these data suggested positive effects on cell-mediated immunity [38].

In a larger clinical trial with 256 patients undergoing major abdominal surgery, length of stay was reduced by ~21% in patients randomized to a fish oil containing lipid emulsion beginning immediately post-surgery and continuing for 5 days compared to the Intralipid control group[37]. Patients and care providers were blinded as to the formulation received. These data provide evidence of safety as well as considerable therapeutic benefits from fatty acid administration. These data are in accord with evidence summarized by Calder[39] showing that fish oil shortened length of hospital stay in some, but not all, of the relevant studies. Thus, a number of studies suggest that omega-3 can benefit postsurgical inflammation and physical function.

In sum, data on the therapeutic administration of fatty acids to promote wound healing and post-operative surgical recovery are highly encouraging. Although some studies in this area have relatively small sample sizes, these provide valuable information regarding mechanistic pathways by which fatty acid interventions exert health benefits. These data are complemented by results from larger studies that provide strong evidence for the safety and clinical benefits of such interventions. Across studies, the application of randomized assignment and blinded or double-blinded designs speaks to the overall quality of this literature.

CONCLUSION

In summary, inflammation is an important response to wounding. However, excessive or prolonged inflammation can be quite hazardous. Surgery is a stressful experience, and psychological stress can substantially slow wound healing and lower production of cytokines at the wound site, while simultaneously enhancing systemic production of proinflammatory cytokines[11, 34]. The omega-3 PUFAs have positive effects on both depression and inflammation, supporting their potential importance in the surgical and critical care arenas. Further research is clearly needed on this very important topic.

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