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Biobehavioral Mechanisms Associated With Nonhealing Wounds and Psychoneurologic Symptoms (Pain, Cognitive Dysfunction, Fatigue, Depression, and Anxiety) in Older Individuals With Chronic Venous Leg Ulcers

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Abstract

The prevalence and incidence of chronic venous leg ulcers (CVLUs) are increasing worldwide, as are the associated financial costs. Although it has long been known that their underlying etiology is venous insufficiency, the molecular aspects of healing versus nonhealing, as well as the psychoneurologic symptoms (PNS; pain, cognitive dysfunction, fatigue, depression, and anxiety) associated with CVLUs remain understudied. In this biobehaviorally focused review, we aim to elucidate the complex mechanisms that link the biological and molecular aspects of CLVUs with their PNS. Innovations in "omics" research have increased our understanding of important wound microenvironmental factors (e.g., inflammation, microbial pathogenic biofilm, epigenetic processes) that may adversely alter the wound bed's molecular milieu so that microbes evade immune detection. Although these molecular factors are not singularly responsible for wound healing, they are major components of wound development, nonhealing, and PNS that, until now, have not been amenable to systematic study, especially over time. Further, this review explores our current understanding of the molecular mechanisms by which the immune activation that contributes to the development and persistence of CVLUs also leads to the development, persistence, and severity of wound-related PNS. We also make recommendations for future research that will expand the field of biobehavioral wound science. Biobehavioral research that focuses on the interrelated mechanisms of PNS will lead to symptom-management interventions that improve quality of life for the population burdened by CVLUs.

Keywords

chronic wounds, chronic venous ulcers, biobehavioral mechanisms, aging, symptoms

Chronic venous leg ulcers (CVLUs) are associated with the symptom burden related to a wound, including aching, wound pain, tightness, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction (Eklöf et al., 2004). Emerging evidence indicates that individuals with CVLUs, along with moderate-to-severe pain, may also have high levels of fatigue, depression (Hellström, Nilsson, Nilsson, & Fagerström, 2016), and anxiety (Do, Edwards, & Finlayson, 2016; Edwards et al., 2014), a symptom cluster collectively known as psychoneurologic symptoms (PNS). These symptoms further contribute to patients' diminished quality of life and inability to participate in disease self-management and affect their functional status and work patterns so often that

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many patients must resort to early retirement (Hansen, Feuerstein, Calvio, & Olsen, 2008). Unfortunately, current treatment models tend to focus only on treating the leg ulcer in isolation instead of examining the multilevel variables that cause symptoms and nonhealing.

In this article, we provide an overview of the evolving theory of the biobehavioral basis of CVLUs. Our central hypothesis is that the interrelated cellular and molecular mechanisms whose immune activation contributes to the development and persistence of CVLUs may also lead to the development and severity of PNS. Our hope is that future biobehavioral research that focuses on the interrelated mechanisms of PNS associated with CVLUs will lead to the development of interventions for symptom management that will improve quality of life for affected patients.

Overview of Chronic Venous Leg Ulcers

Epidemiology

CVLUs, which account for 70–90% of ulcers found in the lower leg, affect 2 million persons annually, including nearly 4% of people over the age of 65 years (Margolisa, Bilkerb, & Santannab, 2002). CVLUs are a particular threat to older individuals, as peak prevalence occurs in those 60–80 years of age (Margolisa et al., 2002), and increased age is a major risk factor for impaired wound healing (Guo & Dipietro, 2010). In the United States, CVLU treatment costs are nearly $2.5 billion a year, which comprises as much as 1% of total health-care costs (Nelzen, 2000), earning CVLUs the label of a "snowballing threat to public health and the economy" (Sen et al., 2009). Unfortunately, despite their prevalence and cost, CVLUs remain an underrecognized and undertreated disease (Henke, 2010; Kolluri, 2014).

CVLUs are associated with multiple comorbidities (e.g., diabetes, obesity, cardiovascular disease) and are rarely seen in individuals who are otherwise healthy (Sen et al., 2009). Risk factors for CVLUs include older age, female sex, obesity, trauma, congestive heart failure, immobility, congenital absence of veins, deep vein thrombosis, phlebitis, family history of leg ulcers, multiple pregnancies, and Factor V Leiden mutation (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Do et al., 2016; Edwards et al., 2014; Vasudevan, 2014).

Venous Ulcer Formation

Venous reflux and obstruction contribute to the pathophysiology of chronic venous disease (CVD), which causes venous hypertension and, ultimately, venous ulcers in individuals with genetic and environmental risk factors (O'donnell et al., 2014; see Figure 1). Venous hypertension may lead to calf-pump incompetence, which results in blood stasis, capillary damage, and edema and skin hypoxia. Increased hydrostatic pressure leads to increased venous pressure and inflammation within the vein walls and valves and also moves inflammatory cells and molecules into the interstitial space. This dramatic inflammatory response activates leukocytes, primarily macrophages and monocytes, as well as T lymphocytes and mast cells (Raffetto, 2018). In addition, inflammatory modulators and chemokines, cytokines, growth factors, matrix metalloproteinases (MMPs), and regulatory pathways participate in the inflammatory response, leading to CVD and CVLUs.

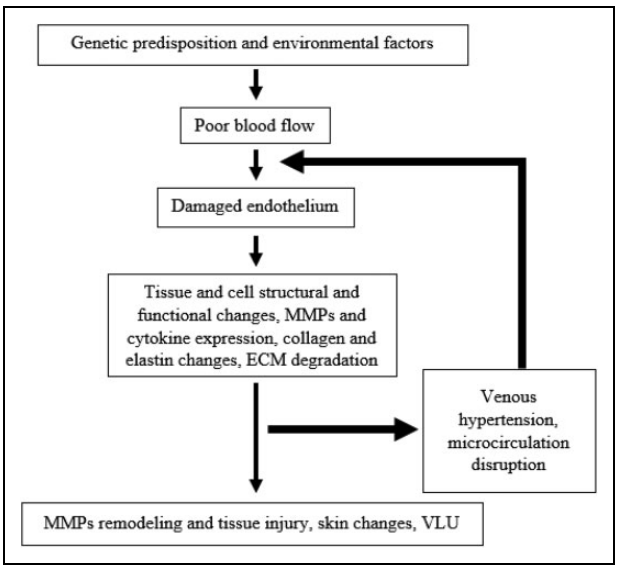

Figure 1. Schematic flow diagram of chronic venous disease pathophysiology. ECM = extracellular matrix; MMPs = matrix metalloproteinases; VLU = venous leg ulcer. Adapted from Raffetto (2018).

Characteristics of CVLUs

A venous ulcer is a full-thickness defect of the skin (confirmed via venous duplex ultrasound testing), most frequently in the ankle region, that fails to heal spontaneously, is sustained by CVD, and tends to become chronic (Lal, 2015). A CVLU is defined as an open lesion between the knee and the ankle joint that remains unhealed for at least 30 days (Baker, 2007; Tatsioni, Balk, O'Donnell, & Lau, 2007) and occurs in the presence of venous disease (Baker, 2007). A majority of patients with venous leg ulcers will have recurrences and ulcer durations of >1 year (Ruckley, 1997). CVLUs are also characterized by a prolonged inflammatory response with unbalanced cellular and molecular components within the wound microenvironment (Gould et al., 2015; Schramedei et al., 2011).

Chronic-wound microenvironment. The microenvironment of a wound is the setting for an ongoing bidirectional interaction among cells and the surrounding biochemical, biophysical, and cellular responses to injury regulating tissue regenerative responses. Interactions between cells and the extracellular matrix (ECM) guide and regulate cellular morphology, differentiation, migration, proliferation, and survival during tissue repair (Scalise et al., 2015; Schultz, Davidson, Kirsner, Bornstein, & Herman, 2011; Zenilman et al., 2013). Increased levels of inflammatory molecules, including pro-inflammatory cytokines and C-reactive protein (CRP), have been identified as components of chronic-wound environments (T. Liu, Yang, Li,

Table 1. Biological and Chemical Factors Involved in the Inflammation and Healing of a Venous Ulcer.

Biological or Chemical Factor	Role in Inflammation and Healing	Activity in Chronic Venous Ulcers	Outcome of Activity
C-reactive protein	Blood marker for inflammation in the body	Increased during inflammation	Signal of inflammation
Cytokines	Small secreted proteins that can be either pro- or anti-inflammatory	During inflammation, pro-inflammatory cytokines are increased, while anti-inflammatory cytokines are decreased	Increased pro-inflammatory cytokines enhance the inflammatory process
Interleukins	A group of glycoproteins (cytokines) produced by leukocytes that regulate immune responses	Increased during inflammation	Promotion of the inflammatory process
IL-1β	Pro-inflammatory cytokine that initiates inflammatory mediators (increases MMPs)	Increased during inflammation	Damage to ECM and vascular endothelium
TNF-α	Pro-inflammatory cytokine that initiates inflammatory mediators (increase MMPs)	Increased during inflammation	Damage to ECM and vascular endothelium
MMPs	Proteases that degrade collagen and collagen fragments	Increased during inflammation	Damage to ECM and vascular endothelium
TIMP	Protein regulator that inhibits the activity of MMPs	Reduced during inflammation	Reduced concentration of TIMPs leads to increased concentration of MMPs and prolonged inflammation
Proteases	Enzymes that break down proteins and peptides	Increased during inflammation	Prolonging of inflammation and damage to ECM
Neutrophils	Neutrophilic white blood cells generate free radicals, debride ulcer via secretion of proteolytic enzymes, and phagocytose the dead bacteria and matrix debris	Increased during inflammation	Production of excess proteases and increased tissue damage
Fibroblasts	Biological cells that synthesize ECM and collagen	Increased during healing	Formation of granulation tissue, which leads to healing
Macrophages	White blood cells that secrete growth factors, chemokines, and cytokines and also clean up nonfunctional host cells, bacteria-filled neutrophils, damaged matrix, foreign debris, and remaining bacteria	Increased during inflammation	Secretion of pro-inflammatory cytokines increases MMP production, reduces TIMPs, and reduces collagen synthesis, which promotes inflammation. However, growth-factor secretion should resolve inflammation and promote healing.
Eosinophils	White blood cells that are activated during allergic reactions, autoimmune disease, and parasitic infections	Increased during inflammation	Increase in tissue damage
Reactive oxygen species	Oxygen-containing chemically reactive species, overproduction of which can lead to oxidative damage and increased production of serine proteases, MMPs, and inflammatory cytokines	Increased during inflammation	Increased damage to ECM and cell membrane and premature cell deterioration
Hypochlorous acid	Chemical inhibitor of TIMPs	Increased during inflammation	Wound-tissue degradation
N-chloramines	Chemical inhibitor of TIMPs	Increased during inflammation	Wound-tissue degradation

Note. ECM = extracellular matrix; IL = interleukin; ROS = reactive oxygen species; TIMP = tissue inhibitor of metalloproteinases; TNF = tumor necrosis factor; MMPs = matrix metalloproteinase.

Yi, & Bai, 2014), and researchers have identified significantly elevated levels of both CRP and interleukin-6 (IL-6) in wound fluid (Ligi, Mosti, Croce, Raffetto, & Mannello, 2016). MMPs, or extracellular proteases, can also thwart or support wound healing. While low levels of MMPs are necessary for healing, high levels contribute to a molecular mechanism that prevents wounds from healing (Simpson et al., 2013). In one study, higher MMP levels were also associated with more severe pain (Raffetto, Mosti, Santi, Ligi, & Mannello, 2015; see Table 1). Most studies, though, have not measured these components of the wound environment concurrently and/or over time (Broszczak, Sydes, Wallace, & Parker, 2017). Emerging evidence from studies using high-throughput techniques, including gene sequencing, indicates that chronic wounds are susceptible to complex bioburden, which facilitates the development of microbial biofilms in the wound microenvironment.

Biofilms. Biofilms are permanently aggregated microbial cells on a variety of surfaces (Donlan, 2002). Once accumulated, these cells are hard to remove because they are protected by a tough enclosure made predominately of polysaccharide casing and other nearby material. A biofilm's morphology depends not only on the surrounding environment but also on the type of wound. Compared to chronic wounds, acute wounds are significantly less likely to have biofilms, and the biofilms that do form on acute wounds are morphologically different from those that form on chronic wounds (James et al., 2008).

There is no general agreement as to how biofilms affect chronic wounds and prevent healing (Bjarnsholt et al., 2008; James et al., 2008; Percival, Hill, Malic, Thomas, & Williams, 2011; Wolcott, Rhoads, & Dowd, 2008). Conclusions have been limited by small sample sizes and different treatment regimens across studies (G. S. Lazarus et al., 2016; Y. C. Liu, Margolis, & Isseroff, 2011). In addition, there are no relevant animal models that reflect the chronic-wound environment in humans (Ansell, Holden, & Hardman, 2012). Exploration of the functional complexity of a wound's microenvironment would lead to an increased understanding of the associations of host factors, comorbidities, and systemic inflammation with the symptom clusters that accompany the impaired wound-healing process (Scalise et al., 2015).

Symptom Clusters Associated With CVLUs

Researchers have determined that a number of concurrent symptoms are highly prevalent in individuals with CVLUs (Edwards et al., 2014; Kelechi, Mueller, & Dooley, 2017). In fact, the majority of patients experience four or more concurrent symptoms, which frequently include pain, fatigue, depression, leg swelling, and sleep disturbances. Thus, researchers have begun considering the interrelationship between PNS and chronic wounds, questioning whether some or all of the PNS might share biological mechanisms (Cleeland et al., 2003) and hypothesizing that these mechanisms might also underlie the chronicity of the wounds (Dodd et al., 2001). One well-validated, integrative biobehavioral paradigm links the adverse effects of inflammation to multiple health outcomes, including high levels of PNS (Do et al., 2016; Reuben et al., 2002), excess morbidity and mortality in multiple chronic conditions (Cryan & Dinan, 2012; Miller et al., 2000), and aging (Reuben et al., 2002). With recent technological advances in the use of biomarkers, researchers are becoming increasingly interested in understanding how the interactions among multiple systems contribute to the immune system's inflammatory response and PNS.

Pain

Pain commonly affects individuals with CVLUs and greatly complicates their disease self-management (Alföldi, Wiklund, & Gerdle, 2014) by causing delays in treatment and reducing these patients' overall functioning and quality of life (Althaus et al., 2012; Edwards et al., 2014; Haythornthwaite, Menefee, Heinberg, & Clark, 1998; Kelechi et al., 2017; Poobalan et al., 2003; Saxe, Smith, & McNerney, 2013). Pain associated with CVLUs is often not adequately assessed or managed and is related to diminished quality of life and delays in wound healing (Edwards et al., 2014; Lal, 2015; Raffetto, 2018).

Cognitive Dysfunction, Fatigue, Depression, and Anxiety

In addition to condition-specific symptoms, many individuals with chronic diseases such as CVLUs experience cognitive dysfunction, fatigue, depression, and anxiety that may co-occur with pain (Kelechi et al., 2017). These symptoms go hand in hand with pain because of cognitive processes that may influence pain perception and bias nociceptive processing in the brain (Wiech, Ploner, & Tracey, 2008) and because chronic pain, anxiety, and depressive symptoms may impair cognitive abilities (Seminowicz & Davis, 2007).

In a recent study, 42% of depressed and anxious participants reported difficulties with memory and concentration, while less than 8% of medical controls experienced the same symptoms (Saffer, Lanting, Koehle, Klonsky, & Iverson, 2015). For individuals and families affected by serious comorbidities, PNS may be particularly overwhelming because they affect the mental and emotional processing that is crucial for disease self-management. Furthermore, there is increasing evidence that individuals with chronic wounds experience both event-related pain and somatic pain (Rosique, Rosique, & Farina Junior, 2015) and that inflammation and pain can delay healing (Soon & Acton, 2006). Depression has also been associated with delayed wound healing (Cole-King & Harding, 2001; Kiecolt-Glaser & Glaser, 2002). Although research has demonstrated that pain and cognitive/affective symptoms contribute to outcomes in CVLUs, to date there has been little research focusing on symptoms in individuals with CVLUs outside of studies of wound-related pain.

Biobehavioral Mechanisms of CVLU Symptom Clusters

Innovations in "omics" research have increased our understanding of important wound microenvironmental factors (e.g., local inflammation, microbial pathogenic biofilm, epigenetic processes through microRNAs) that adversely alter the wound bed's molecular milieu so that microbes evade immune detection. Although these molecular factors are not singularly responsible for wound healing, they are now recognized as major components of wound development and nonhealing as well as associated PNS that, until now, have not been amenable to systematic study, especially over time.

Meanwhile, innovations in genomics have also advanced our understanding of debilitating chronic symptoms such as pain, fatigue, anxiety, and sleep disturbance. For individuals living with CVLUs, both the immune and central nervous systems may contribute to the development and progression of this symptom burden. Research has demonstrated that the immune system plays an important role in brain function,

bidirectionally communicating with the brain via cytokines, resulting in effects on symptoms (Kipnis, 2018). In fact, studies have shown that inflammation and cytokine levels correlated with symptoms (e.g., stress, pain, decreased appetite, increased sleep, social isolation).

Immune System

Inflammation and wound proteome. Hundreds of proteins, including cytokines, interleukins, and MMPs (Broszczak et al., 2017; Edsberg, Wyffels, Brogan, & Fries, 2012), make up the wound-fluid proteome of both healing and inflamed, nonhealing wounds (Broszczak et al., 2017; Edsberg et al., 2012; Eming et al., 2010; Ganesh et al., 2012; Grieb et al., 2012; Krisp et al., 2013; Ruzehaji et al., 2012; Shah, Omar, Pai, & Sood, 2012; Steinsträßer et al., 2010; Wyffels et al., 2010). Chronic wounds are characterized by increased protease activity, which is primarily caused by fibroblasts, macrophages, eosinophils, and neutrophils releasing elevated levels of MMPs, which eventually degrade the ECM (Broszczak et al., 2017). The activity of the MMPs becomes uncontrollable as their inhibitors, the tissue inhibitors of metalloproteinases (TIMPs), become unable to provide equilibrium, which then results in a wound that gets "stuck" in a prolonged inflammatory state. Bacterial proteases further contribute to the protease activities, which hinders the normal healing processes.

Pro-inflammatory cytokines also play a major role in delayed wound healing and a chronic wound state. IL-1β and tumor necrosis factor-α (TNF-α) are the two leading cytokines that initiate the release of inflammatory mediators, which damage the endothelium. Neutrophils attached to the endothelium are then able to invade the wound and produce reactive oxygen species, which further contribute to tissue damage within the wound bed. Neutrophils also produce hypochlorous acid and N-chloramines, which can effectively inhibit the TIMPs' actions, further contributing to wound-tissue degradation. It is thus important to continue studying the differential expression and activity of proteins in wounds during the phases of inflammation and wound healing and to also understand how they affect wound healing (Broszczak et al., 2017).

Inflammation and wound metabolomics. Metabolomics is the identification and quantification of metabolites generated as a result of cellular physiology at a fixed point in time (Broszczak et al., 2017; Idle & Gonzalez, 2007). It can provide a snapshot of cell and tissue metabolism in an inflamed wound. Examples of metabolites include vitamins, carbohydrates, lipids, steroids, amino acids, nucleic acids, and peptides (Arakaki, Skolnick, & McDonald, 2008; Broszczak et al., 2017; Zhou, Xiao, Tuli, & Ressom, 2012). These biomolecules are ideal for use as biomarkers when diagnosing clinical states including inflammation. Given the recent adoption of high-throughput methods for metabolomics inquiry, we are still early in our metabolomics investigations of CVLUs. Metabolites currently of interest in this field of study include L-arginine, nitric oxide, oxidative free radicals, and iron, each of which has been found to be significantly elevated within the chronic-wound environment and directly associated with inflammation. Future research is necessary to more fully explore the chronic-wound metabolome.

Central Nervous System

Although still in its early stages, the emerging field of psychoneuroimmunology provides a mechanism for studying the brain's response to immunological information; the resulting knowledge may advance our understanding of PNS (Kipnis, 2018). New findings indicate that the immune system and the brain interact constantly during health and illness. Kipnis (2018) showed that, by actively detecting microorganisms in the body and informing the brain about their presence, the immune system assists the brain in dealing with stress and in developing sickness behaviors. One of the most characteristic of these behaviors is fatigue (Abbas, Jorgensen, & Lindor, 2010; Menzies et al., 2015; Newton, 2010), often accompanied by increased sedentarism and sleep disturbance (Newton & Jones, 2012). Sickness behaviors are also associated with cognitive changes (Elliott, Frith, Pairman, Jones, & Newton, 2011; Lee, Otgonsuren, Younoszai, Mir, & Younossi, 2013; Newton, Pairman, Wilton, Jones, & Day, 2009; Weinstein, 2011). Intensive study to better understand the linkages among inflammatory mediators and behavioral outcomes is ongoing across multiple acute and chronic medical conditions.

Perceived psychological stress leads to an inflammatory response and activation of the hypothalamic–pituitary–adrenocortical (HPA) axis through increased release of cortisol and catecholamines (Menzies et al., 2015). Increased psychological stress can also induce elevations in the levels of pro-inflammatory cytokines, which suggests a direct link between stress and inflammation (Menzies et al., 2015) and is associated with delayed wound healing (Kiecolt-Glaser, Marucha, Mercado, Malarkey, & Glaser, 1995).

Implications for Biobehavioral Research

Given the shared symptoms among many individuals with CVLUs, researchers agree that common, related mechanisms may be at work in chronic wounds (Menzies et al., 2015). Extensive findings suggest bidirectional relationships among host factors that affect the immune system, the microenvironment of the wound, inflammation, PNS and other symptoms, and the healing trajectory of CVLUs (Dantzer et al., 2008; Do et al., 2016; Edwards et al., 2014; Gould et al., 2015; Guo & Dipietro, 2010; Han et al., 2011; Hareendran et al., 2005; Hellström et al., 2016; Lai & Siu, 2014; Lal, 2015; G. S. Lazarus et al., 2016; Ligi et al., 2016; Y. C. Liu et al., 2011; Mann & Mann, 2013; Margolis, Bilker, Santanna, & Baumgarten, 2002; Raffetto et al., 2015; Ruckley, 1997; Sarkar & Fisher, 2006; Sisco et al., 2008; Wang et al., 2012; Watters et al., 2013; Zhao et al., 2013). Based on the existing research, we propose that a wound's microenvironmental components, which include local inflammation and biofilm, trigger both a local and a systemic

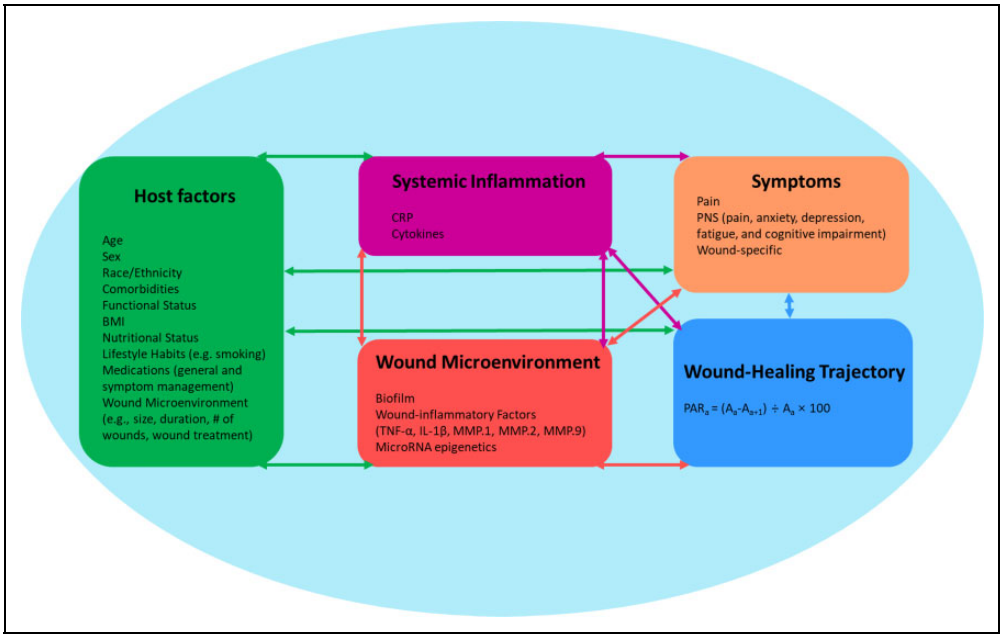

Figure 2. Putative mechanisms underlying the symptom experience in chronic venous leg ulcers (CVLUs). Several simultaneously occurring biological mechanisms likely contribute to the development of the symptom cluster. Inflammation and biofilm contribute to the development and progression of CVLUs. The central and autonomic nervous systems respond to stress, whether psychological or physiological (i.e., inflammation). With this response comes with further immune-system activation with the potential for delayed wound healing. The co-occurring symptoms of CVLUs have a potential bidirectional relationship with the immune system within the microenvironment of the wound and also systemically. BMI = body mass index; CRP = C-reactive protein; IL-1β = interleukin-1β; MMP = matrix metalloproteinase; PAR = percent area reduction (in the equation, A = area of the wound at a given time); PNS = psychoneurologic symptoms; TNF-α = tumor necrosis factor-α. Adapted from Raffetto (2018).

host inflammatory reaction (Han et al., 2011; Zhao et al., 2013) that may lead to further biological perturbations such as epigenetic alterations and symptoms (Bavan & Midwood, 2011; Das, Ganesh, Khanna, Sen, & Roy, 2014; Lai & Siu, 2014; Madhyastha, Madhyastha, Nakajima, Omura, & Maruyama, 2012; Mann & Mann, 2013; Robinson et al., 2013; Sisco et al., 2008; Wang et al., 2012; Watters et al., 2013). Figure 2 depicts a conceptual framework describing the potential mechanisms underlying the common symptoms experienced by older adults with CVLUs.

Host Factors

We propose that patient host factors (e.g., age, disease burden, sex, race/ethnicity, body mass index, nutritional status, lifestyle habits including smoking) affect all other factors in the model. Demographic characteristics and age are related to increased incidence and prevalence of CVLUs. In addition, multiple studies have shown sex-related differences in wound healing (Ligi et al., 2016) and outcomes.

Sex. In a recent study, researchers showed that symptom clusters differed between women and men with VLUs: The top three symptoms for women, in order of frequency, were achy legs, swelling, and pain, while for men, they were swelling, achy legs, and heavy legs. Women described their symptoms as being primarily hurting and annoying, while men described theirs as nagging and irritating (T. Liu et al., 2014).

Aging. Older aged people experience an increased abundance of pro-inflammatory cytokines and a lower count of growth factors. Pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-α) tend to sustain inflammation, while growth factors (e.g., endothelial growth factor, fibroblast growth factor-2, transforming growth factor-β, platelet-derived growth factor, and vascular endothelial growth factor) combat inflammation via reepithelialization (Kurosaka et al., 2009). Unlike relatively healthy patients with acute wounds in which growth factors and cytokines are increased, patients with chronic wounds experience decreased levels of growth factors and increased levels of pro-inflammatory cytokines (Barrientos, Stojadinovic, Golinko, Brem, & Tomic-Canic, 2008). Further, patients with CVLUs experience even greater reductions in cell growth and healing than might be expected based solely on their reduced levels of growth factors because their fibroblasts are not as reactive to growth factors' stimuli as are those of healthier patients (Ågren, Steenfos, Dabelsteen, Hansen, & Dabelsteen, 1999; Falanga, Zhou, & Yufit, 2002; Kim et al., 2003).

Overexpression and increased activity of MMPs in older adults can also delay healing. MMPs, which increasingly degrade collagen and collagen fragments, can be upregulated by certain hormonal changes that are characteristic in older adults. For example, higher levels of norepinephrine in older

patients (Veith, Featherstone, Linares, & Halter, 1986; Yang et al., 2006) and lower levels of estrogen in postmenopausal women (Ashcroft, Greenwell-Wild, Horan, Wahl, & Ferguson, 1999) can elevate levels of MMPs, leading to sustained inflammation.

Similar to MMPs, neutrophil elastase breaks proteins and peptide bonds and tends to be more abundant in chronic wounds and older patients (Enoch & Price, 2004). By degrading proteins (e.g., fibronectin, vitronectin, tenascin) that aid in the reformation of the ECM, elastase delays healing and enables inflammation. Furthermore, the response to the work of proteases is slower in older adults due to their bodies' weakened signal transduction, which also contributes to delays in ECM reconstruction and healing (Ashcroft, Mills, & Ashworth, 2002).

Older patients with CVLUs are at additional risk of delayed healing due to the characteristically high iron content of their wounds, which feeds macrophages and stimulates prolonged inflammation (Sindrilaru et al., 2011). These conditions, along with other effects of advanced age, can put a tremendous burden on a body that is attempting to heal.

Comorbidities. It is well established that multiple factors may contribute to inflammatory dysfunction and higher symptom burden across comorbid conditions (Sarkar & Fisher, 2006). However, the underlying mechanisms associated with the trajectory of wound healing in the growing population of older individuals with CVLUs, as well as the ways comorbidities and other factors affect healing outcomes, are virtually unknown (Gould et al., 2015).

Comorbidities are associated with multiple biological perturbations including heightened pro-inflammatory activation and reduced microbial clearance. The host immune system is governed by comorbidities that may affect the wound-healing process, such as diabetes, venous insufficiency, congestive heart failure, abnormal white blood cell function, and obesity (Wolcott et al., 2008). Additionally, healing in patients with chronic wounds can be influenced by medications, antibiotic resistance, additional infected areas, pro-inflammatory wound condition, compromised immunity, poor circulation, poor hydration, and other nutritional deficiencies (Moreo, 2005).

Medications and antibiotic resistance. Chemotherapy medications such as antineoplastic agents (e.g., Eloxatin for metastatic colon cancer) can interfere with wound healing by disrupting cellular replication (Pollack, 1982). Meanwhile, other medications, such as antibiotics (e.g., penicillin), which are still prescribed by some practitioners for CVLUs, may simply be ineffective in treating chronic leg wounds, especially in patients with antibiotic resistance (Howell-Jones et al., 2005).

Additional infected area. When a patient has an additional area of infection (whether viral, bacterial, fungal, or protozoal), the host monocytes are transferred to peripheral tissues including the area of the leg wound. The presence of monocytes and their eventual differentiation into macrophages can further reinforce inflammation and delay healing (Shi & Pamer, 2011).

Pro-inflammatory conditions. Pro-inflammatory conditions, such as rheumatoid arthritis, result in the release of pro-inflammatory cytokines (e.g., IL-1, IL-6, and TNF-α), which, in turn, promote and prolong the inflammatory process (Choy & Panayi, 2001).

Compromised immunity. Healing can also be delayed due to a body's lack of response to pathogens. For example, patients who are HIV-positive with AIDS experience compromised immunity because they have low (<100) CD4+ T-cell counts (Njunda, Nsagha, Assob, Kamga, & Teyim, 2012; Weledji, Kamga, Assob, & Nsagha, 2012). Low counts of these white blood cells means limited protection from infection and, thus, prolonged wound healing (Weledji et al., 2012).

Poor circulation. Patients with circulatory problems (such as in diabetes mellitus) have trouble with tissue repair because their reduced blood flow leads to limited oxygen supply for the wound (Greenhalgh, 2003). Since oxygen is imperative for collagen synthesis by fibroblasts and for tissue regeneration, a limited blood supply can further delay wound healing (Trabold et al., 2003).

Nutritional and hydration deficiencies. While changes in oxygen supply to the wound are not always obvious, the effects of a patient's nutritional intake and digestive process can be more apparent. Patients who have frequent diarrhea from medications for their comorbidities (e.g., omeprazole for heartburn or stomach ulcers, nonsteroidal anti-inflammatories for arthritis, metformin for diabetes) can experience nutrient and hydration deficiencies. Limited hydration and nutrient supply to the wound can hinder many of the processes of healing including epithelialization and collagen synthesis (Stechmiller, 2010).

Obesity. Patients who are obese experience low-grade inflammation, which includes many components of the traditional inflammatory response to pathogens, such as local wounding and systemic increases in cytokines.

Inflammation. Host immune factors (systemic inflammation) and the wound microenvironment affect each other as well as symptoms and wound healing. CRP level, a clinically validated marker of inflammation, is a useful tool for determining the degree of systemic inflammation as well as the effectiveness of treatments. Measuring systemic cytokines can also provide much needed information about the extent of systemic inflammation in older individuals with CVLUs.

CVLU treatments. Studies on treatments for CVLUs have mainly focused on the correction of hemodynamic alterations and compression therapy. Meanwhile, there has been little examination of biological intervention targets (Ligi et al., 2016) such as the presence of biofilm and its impact on

inflammation in the microenvironment and the entire system (Ligi et al., 2016; T. Liu et al., 2014). Consequently, patients with CVLUs are often treated with sequential treatments without an evidence-based rationale for the order or timing of treatment strategies.

Further knowledge regarding the biological characteristics associated with healing and nonhealing are thus especially important for determining the best use of medications, surgery, and other treatments for CVLUs (G. Lazarus et al., 2014). Similarly, the relationship of treatment variables with symptoms has been understudied in individuals with CVLUs, though their excessive symptom burden is well documented (Hareendran et al., 2005; Kelechi & Johnson, 2012).

Trajectory of Chronic-Wound Healing

Healing in a chronic wound is challenging, requiring a complex process of sequential stages including inflammation, reepithelialization, formation of granulation tissue, local revascularization, and remodeling (Järbrink et al., 2016). During epithelialization, cellular mechanisms are responsible for keratinocyte migration and proliferation, which are essential for successful wound closure. If keratinocytes fail to close the wound and maintain a barrier, chronicity and wound recurrence are likely to occur. Thus, unsuccessful reepithelization characterizes a nonhealing chronic wound (Rousselle, Braye, & Dayan, 2018).

Multiple pathophysiologic factors prevent a chronic wound from reepithelializing and maintaining closure. Those associated with the chronicity of VLUs include venous hypertension, infection, biofilms, malnutrition, age, diabetes and other comorbidities, tissue hypoxia, exudates, excessive levels of inflammatory cytokines and proteases, reactive oxygen species, and senescent cells (Rousselle et al., 2018). Studies have shown that older adults burdened with CVLUs have low keratinocyte-cell activity, which contributes to delayed reepithelialization (Grove & Kligman, 1983).

To accurately monitor the wound-healing trajectory in clinical research, investigators must precisely document the wound size (i.e., perform assessment of the wound area; Bowling, Paterson, & Ndip, 2013). Recent innovations in three-dimensional wound imaging have enhanced the ability to compute the curvature of the wound through analysis of laser-beam traces (Foltynski, Wojcicki, Ladyzynski, & Sabalinska, 2014). Specifically, the Silhouette, a handheld device that minimizes variability between wound measurements, provides laser-enhanced accuracy in the measurement of a wound's length, width, and depth, while advanced software makes other calculations including volume (Casas, Castaneda, & Treuillet, 2011; Nixon & Moore, 2016). The Silhouette has demonstrated a high level of reliability, validity, and reproducibility across studies (Casas et al., 2011; Foltynski et al., 2014; Nixon & Moore, 2016).

Future Interventional Research Involving Biobehavioral Mechanisms and PNS

Future research exploring shared biobehavioral mechanisms of wound chronicity and PNS would not only expand our understanding of these mechanisms and associated symptoms but would also lead to the development of nursing and other targeted interventions that could improve symptom management and quality of life (Menzies et al., 2015). Psychosocial and behavioral nursing interventions that aim to reduce chronically ill patients' stress, strengthen their self-management skills, and enhance their coping skills have the potential to reduce CNS overload and cytokine dysregulation and, subsequently, to improve patients' quality of life. For example, studies of strategies such as mindfulness-based stress reduction meditation programs have demonstrated decreased levels of stress, reduction in Th1 (pro-inflammatory cytokines, and enhanced quality of life in other diseases; Carlson, Speca, Faris, & Patel, 2007; Menzies et al., 2015). To date, however, no studies have examined the influence of such interventions on the symptom experience in individuals with CVLUs. Behavioral interventions such as physical activity or exercise, weight loss, smoking cessation, and diet modification could also improve the physiological aspects of CVLUs and patients' level of functioning (Bergasa, Mehlman, & Bir, 2004; Menzies et al., 2015; Promrat et al., 2010). However, whether or not these interventions affect the symptom experience has yet to be explored (Menzies et al., 2015).

Conclusion

The similarity in symptom experiences across patients with CVLUs suggests that there may be pathophysiological processes in common between these nonhealing wounds and symptoms. In other words, these findings suggest the presence of symptom clusters associated with CVLUs. With the growing number of individuals living long term with CVLUs, it is crucial that we develop a better understanding of the biological underpinnings of these symptom clusters so that we may begin to develop more targeted and effective symptom-management strategies. Recent gains in knowledge regarding communication between the brain and the immune system open new opportunities for nurse-researchers to examine interdependent and possibly synergistic interactions among biological and behavioral factors, symptom clusters, and outcomes in CVLUs.

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Author Contributions

Joyce K. Stechmiller contributed to conception, design, acquisition, analysis, and interpretation; drafted manuscript critically; revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Debra Lyon contributed to conception, design, acquisition, analysis, and interpretation;

drafted manuscript critically; revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Gregory Schultz contributed to conception, design, acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Daniel J. Gibson contributed to design, acquisition, analysis, and interpretation; drafted manuscript critically; revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Michael T. Weaver contributed to conception, design, analysis, and interpretation; drafted manuscript critically; revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Diana Wilkie contributed to conception, acquisition, analysis, and interpretation; drafted manuscript critically; revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Anastasiya V. Ferrell contributed to conception, acquisition; drafted manuscript critically; revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Joanne Whitney contributed to conception, acquisition; drafted manuscript critically; revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Junglyun Kim contributed to conception, design, and acquisition; drafted manuscript critically; revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Susan B. Millan contributed to design and acquisition; drafted manuscript critically; revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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