REVIEW ARTICLE

Treat the Whole Not Just the Hole: Holistic Wound Care Approach

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KEYWORDS:
Hypercoagulable State
Hypothyroidism
Obstructive Sleep Apnea
Ulcers
Wounds

ABSTRACT: The key to successful wound care lies in the provider's ability to accurately identify etiology of the wounds and recognize factors that may contribute to their chronicity. Some of the most commonly encountered and clinically significant barriers include macro- or micro-angiopathic diseases, infection, protein-energy malnutrition, smoking, and metabolic disorders. In this article, we evaluate a case of chronic non-healing wounds in a patient with hypothyroidism, Factor V Leiden mutation, and obstructive sleep apnea. Attention is drawn to the impact of these comorbid conditions on integrity and regeneration of soft tissues, both from pathophysiological and histological aspects.

INTRODUCTION

Long-standing wounds are crippling physically, psychologically, and emotionally. Understanding biochemistry of healing and factors that facilitate or impede this process is essential. Chronic wounds often regain their positive healing trajectory when etiology and contributing factors are correctly identified and adequately managed.[1]

CASE PRESENTATION

44-year-old male with history of morbid obesity, peripheral vascular disease, lymphedema, and multiple episodes of bilateral lower extremity (b/l LE) cellulitis came to our clinic for a second opinion. His chief complaint was chronic non-healing b/l LE wounds that started twelve years prior after a trip-related DVT. Patient reported having profuse drainage, malodor, swelling and pain in both legs. His independence, lifestyle, and ability to work were greatly affected. Review of systems revealed weight gain, lack of energy, and tiredness.

Surgeries included bilateral hip arthroplasties due to congenital hips dysplasia, right foot trans-metatarsal amputation due to invasive infection, and has right lower extremity vein stripping in 1994. He is married and has one daughter; denied tobacco, alcohol, or illicit drugs use. His family history revealed an unknown hypercoagulable disorder in this mother.

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 Print ISSN: 1877-573X

WOUND CARE TREATMENT

Due to lymphedema and chronic venous insufficiency, the main stem of his treatment was compression therapy with multi-layer compression wraps and pneumatic compression devise. Adding energy-based modalities, such as ultraviolet C light, electrical stimulation, and high-frequency megahertz ultrasound did not show robust changes. Due to his chronic lymphorrhea and high propensity to soft tissue infection, we used antimicrobial absorptive dressings. Sharp debridements were employed on as needed basis. Bioengineered skin substitute, such as Apligraf, was utilized twice. Although complete wound closure was not achieved, we were able to control his pain, profuse drainage, and malodor.

PATIENT EVALUATION

Detailed history, thorough physical exam, differential diagnoses, and appropriate work up are critical components of the initial evaluation. Our patient had mentioned significant weight gain, lack of energy, and tiredness, which prompted further testing and laboratory work up and revealed an elevated thyroid stimulating hormone (TSH) level, Factor V Leiden deficiency and obstructive sleep apnea.

WOUNDS AND HYPOTHYROIDISM

Prevalence of hypothyroidism, both overt and subclinical, is up to 9.5% of the general population as reported in the prevalence studies.[2,3] Hypothyroidism is associated with hyperlipidemia,[4] cardiovascular disease,[5] and depression;[6] however, it has also been shown by numerous studies to have direct[7-24] and indirect effect on wound healing.[25-28] The impairment of cutaneous wound healing has been demonstrated in hypothyroid states, induced by anti-thyroid drugs,[16,17] thyroid radiation,[12] or surgical ablation.[11]

Hypo-functional thyroid gland directly interferes with fibroblast utility[10,11] prolongs the proliferative phase of healing and alters the quality of collagen, forming thinner and smaller collagen fibers.[12,13,15] Since collagen is the only protein in the body containing hydroxyproline in significant amounts, hydroxyproline became the focus of many studies since the 1960s. It is released with collagen degradation and is excreted in urine.[29] Excretion of hydroxyproline is greatly reduced in hypothyroidism and may be corrected by hormone replacement therapy, thereby normalizing collagen metabolism.[30]

In order to analyze the relationship between hypothyroidism and wound healing, Natori et al. induced a state of severe hypothyroidism in rats and then assayed the levels of hydroxyproline and pro-collagen peptide.[11] He was able to demonstrate significantly decreased levels of type IV collagen and hydroxyproline throughout the inflammatory phase extending to the proliferative phase of healing. These findings suggest that low levels of thyroid hormone cause disturbance in the tissues' metabolic activity and lead to down regulation of collagen production through multiple phases of healing.

At the molecular level, thyroid hormone can act directly on cutaneous tissues by binding to the thyroid hormone receptor.[9, 24] Immunohistochemical localization and quantitative polymerase chain reaction have shown all three thyroid hormone binding receptor isoforms to be expressed in the skin.[31,32] As Safer et al. described it, thyroid hormone receptors have been detected in a variety of cells: epidermal keratinocytes, skin fibroblasts, hair outer root sheath, dermal papilla, fibrous sheath of the hair follicle, arrector pili muscle cells, sebaceous glands, vascular endothelial cells, smooth muscle cells, and Schwann cells.[9]

Saner et al. described a decreased serum zinc level in patients with hypothyroidism.[33] Another study demonstrated positive effect of thyroid hormone replacement therapy with addition of supplemental zinc on wound healing in hypothyroid rats.[17] However, Ekmektzoglou et al., pointed out that zinc, most likely, does not have a direct effect on the amount of collagen synthesis, but rather affects more directly the cross-linking of formed collagen and therefore influences the tensile strength of the wound.[8]

Hypothyroidism is treated systemically by oral administration of levothyroxine. There are multiple works describing topical application of the thyroid hormone analog TRIAC (triiodothyroacetic acid) to the wounds in vivo. Findings show accelerated epidermal proliferation, dermal thickening, hair growth, and even reversal of the dermal atrophy associated with corticosteroids.[20,24,34,35] Topical triiodothyronine has been shown to stimulate growth of both epidermal keratinocytes and dermal fibroblasts; however is dependent on the presence of systemic triiodothyronine.[20]

Indirectly, thyroid dysfunction is associated with recalcitrance of wounds by markedly altering cardiovascular and renal function, leading to fluid retention. Villabona et al. were able to show not only decreased myocardial contractility, cardiac output, and oxygen consumption, but also an increased peripheral resistance as direct effects of hypothyroidism.[25] It was also pointed out that transcapillary escape of albumin into the extravascular space may add to the development of edema.[25,28] Effects of hypothyroidism extend to decrease renal blood flow, glomerular filtration, and solute-free water excretion.[27] Patients with advanced primary hypothyroidism may be hyponatremic and fail to suppress plasma arginine vasopressin with an acute water load.[26] Luckily, the adverse effects of hypothyroidism might be reversed, and the symptoms relieved with the substitutive therapy.

WOUNDS AND HYPERCOAGULABLE STATE

While initially having positive healing trajectory, our patient had a setback when he developed an acute deep vein thrombosis (DVT) in the right lower extremity. Anticoagulation therapy was started, and further work up revealed Factor V Leiden mutation. This hypercoagulable state shed light onto his high recurrence rate despite adequate compression and aggressive wound care.

Hypercoagulable disorders may cause ulcerations, either indirectly because of deep venous thrombosis, or directly by thrombus formation in small arteries, arterioles, capillaries, or venules.[36-38] In fact, Factor V Leiden mutation is associated with increased prevalence of venous leg ulcers.[39,40]

Gaber et al., within a 2-year period examined 100 consecutive patients with leg ulcers for Factor V Leiden mutation. His investigation showed 36% prevalence rate of Factor V Leiden mutation in patients with post-thrombotic leg ulcers.[41] Later, Hafner et al. confirmed these findings in his study of 73 consecutive patients with venous ulcers. He concluded that in post-thrombotic ulcers, the prevalence of the Factor V mutation was 38%. Even patients with non-post-thrombotic venous ulcers showed a moderately elevated prevalence (16%) of Factor V Leiden mutation.[42]

Factor V is a protein of the coagulation system, sometimes referred to as proaccelerin or prothrombin accelerator. In contrast to most other coagulation factors, it is not enzymatically active but functions as a cofactor. Deficiency leads to predisposition for hemorrhage, while some mutations (most notably Factor V Leiden) predisposes for thrombosis.[43]

Factor V Leiden is named after the city Leiden in Netherlands, where it was first identified in 1994 by Bertina et al.[44] Factor V Leiden thrombophilia is characterized by a poor anticoagulant response to activated protein C (APC) and an increased risk for venous thromboembolism (VTE).[45,46] DVT is the most common VTE, with the legs being the most common site.[45]

During healthy coagulation cascade, prothrombin is converted to thrombin, which in turn activates factors V and VII that further accelerate the cascade to form a blood clot. The coagulation process is normally controlled by circulating antithrombin III, and locally by thrombomodulin, an endothelial receptor that binds thrombin. The thrombin-thrombomodulin complex activates protein C, which subsequently inactivates factor V, thereby inhibiting blood clod formation. However, the mutant form of Factor V, Factor V Leiden, is resistant to inactivation by protein C (APC-resistant) and further induces the coagulation cascade. Consequently, the local protection mechanism against thrombosis is not functioning adequately[46,47] (*See Figure 1)*.

After initiation of anticoagulation therapy with Warfarin we noticed marked improvement in the healing rate of our patient. Nevertheless, we observed inverse relationship between the sizes of his ulcers and INR. Occasional sub-therapeutic INR levels (<1.5) have led to further setbacks in his management. Most likely due to microvascular thrombi formation during inadequate

anticoagulation causing local hypoxemia and subsequent volumetric wounds enlargement. Despite the fact that there are no published reports on the relationship of sub-therapeutic INR level and the size of the venous ulcers, convincing clinical data demonstrates the benefit of anticoagulation in prevention of VTE due to Factor V Leiden mutation.[48]

WOUNDS AND OBSTRUCTIVE SLEEP APNEA

The state of wound oxygenation is a key determinant of healing outcomes. Intermittent hypoxia (IH) or periodic exposure to hypoxia interrupted by return to normoxia or less hypoxic conditions occurs in many different diseases, including sleep-disordered breathing manifested as recurrent apneas.[1] Based on the experimental studies conducted by Prabhakar el al., chronic intermittent hypoxia (CIH) leads to accumulation of reactive oxygen species (ROS) and activation of ROS dependent responses, such as altered carotid body function; elevated blood pressure; enhanced release of transmitters and neurotrophic factors; altered sleep and cognitive behavior; and activation of second-messenger pathways and transcriptional factors.[49]

Moreover, obstructive sleep apnea (OSA) directly affects vascular endothelium by promoting inflammatory and oxidative stress while decreasing nitric oxide availability and repair capacity.[50-52] Vasoconstriction is another cause of local tissue hypoxia that leads to the chronicity of wounds in people with OSA. This is due to endothelin, a potent vasoconstrictor that increases within several hours of untreated OSA,[53,54] likely due to hypoxia.[55]

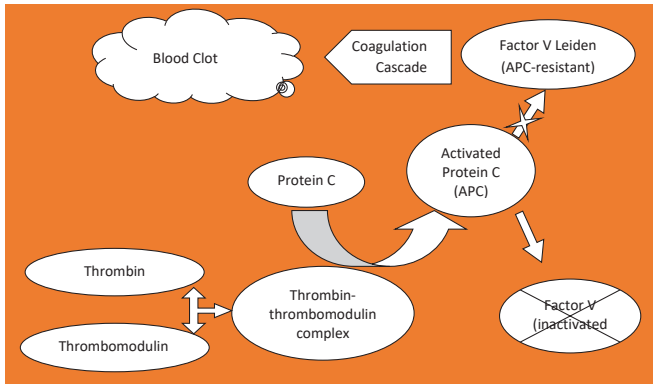
Another interesting fact is the correlation of bilateral lower extremities edema with OSA. Hudgel et al. conducted a three-year investigative research with fifteen patients. All subjects were obese with bilateral pitting leg edema, whose echocardiogram demonstrated pulmonary hypertension only. Despite the small sample size, they were able to trace a correlation between OSA, pulmonary hypertension, and edema. Several possible mechanisms that might lead to edema have been proposed:

- Nocturnal hypoxia activates neuroendocrine system (renin-angiotensin-aldosterone system) and leads to salt and water retention[52,56-58]
- Increased venous and lymphatic hydrostatic pressure due to obesity contributes to swelling
- Secondary pulmonary hypertension caused by intermittent apneic episodes transmits to peripheral venous and lymphatic systems and contributes to edema
- ntermittent right ventricular failure as a result of acute elevations in pulmonary artery pressure during episodes of sleep-associated hypoxia[56]

One of the main treatment criteria of OSA with continuous positive airway pressure (CPAP) is respiratory disturbance index of 5 to 30 events per hour. This should be accompanied by symptoms of excessive daytime sleepiness, impaired cognition, mood disorders, insomnia, or documented cardiovascular diseases: hypertension, ischemic heart disease, or stroke.[59] However, if OSA causes fluid retention and vasoconstriction, then it may be appropriate to expand the indications for treating OSA in patients with accompanying symptoms such as bilateral lower extremity edema, venous stasis ulcers, lymphedema, stasis dermatitis, and cellulitis.[57]

FIGURE 1:

Coagulation Cascade



Chandan Sen conducted sleep screening of 105 patients with chronic wounds and found 51% of them to either have or be at high risk for OSA.[1] Patt et al. carried-out home sleep studies on 50 consecutive patients with unselected chronic lower extremity wounds using an apnea-hypopnea index of 15 events per hour. The results of this study showed the prevalence of OSA to be 57% in patients with wounds.[60]

Much to our surprise, after the initiation of CPAP therapy, pitting edema in our patient had gone down and improvement in ulcer healing was noticed thereafter. Undoubtedly, OSA contributed to the bilateral leg edema and the chronicity of his ulcers. Upon review of the literature, one possible explanation of CPAP benefit in lowering edema in patients with OSA is its effect on aldosterone level. Saarelainen et al. was able to demonstrate that aldosterone and 24-hour mean heart rates decreased during CPAP treatment. Their data also suggested that OSA causes disturbances in blood volume homeostasis which can be corrected by CPAP.[61]

DISCUSSION

Our patient is one of many with chronic, recalcitrant, non-healing wounds. Even though the majority of ulcers are venous, arterial, diabetic, or of mixed etiology, less common conditions should not be missed. This patient is unique and difficult, as the chronicity of his ulcers was perpetuated by multiple problems: morbid obesity, chronic venous insufficiency, lymphedema, hypothyroidism, Factor V Leiden mutation, and OSA.

Despite the prevalence of OSA, by one estimate 1 to 5%[62], the majority of patients with OSA remain undiagnosed. In fact, up to 5% of adults in Western countries are likely to have undiagnosed OSA syndrome, and hence be candidates for treatment.[63] Moreover, approximately one-third of patients with OSA have leg edema at the time of the diagnosis confirmation by polysomnography.[64] Appropriate index of suspicion may aid clinicians to diagnose OSA. Even without traditional signs and symptoms, physical examination findings, such as unexplained pedal edema, recurrent “cellulitis”, and chronic non-healing skin ulcers may facilitate the diagnosis and improve rates of detection of OSA.

Clinical signs of hypercoagulable state, such as repeated thrombophlebitis or unexplained thrombosis, in view of a positive family history of blood clots, are an indication for screening for clotting disorders. Initial laboratory screening tests usually include coagulation profile (PT/PTT/INR), Factor V Leiden mutation, Factor II (prothrombin) mutation, antithrombin III, proteins C and S, lupus anticoagulant, and anticardiolipin.[47]

Finally, consider hypothyroidism as a contributing factor to uncontrolled edema. If this complex metabolic disease treated properly and in a timely fashion, one could reverse the tissue damage, facilitate healing, and improve patient's functional capacity.

AUTHOR DISCLOSURES:
No relevant financial affiliations

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