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The Relationship Between Nutrition and the Speed of Wound Healing in Acute Wound Patients: A Literature Review

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ABSTRACT

Wound healing is a complex but essential physiological process that restores the skin's structure after enduring injuries due to surgical procedures or accidents. Based on the World Health Organization (WHO), the prevalence of wound patients is 1,67 per 1000 people, with a rising prevalence in Indonesia. This process involves three stages which are the inflammatory phase, proliferative phase, and remodeling phase. Many factors play a role when affecting the speed of wound healing in patients, one of which is nutrition. Literature reviews regarding the effects of nutrition specifically zinc, iron, and vitamin E are still limited, leading to this study to be conducted.

Keywords: wound healing; zinc; iron; vitamin E.

INTRODUCTION

Wound healing is a critical physiological process essential for maintaining the skin's structural integrity following trauma caused by accidents or medical interventions. The skin serves as a vital barrier protecting internal organs from external harm, and significant injuries to the skin can lead to long-term health complications. The prevalence for wounds based on the World Health Organization (WHO), there are 1,67 per 1000 people. According to data from RISKESDAS (2018), the prevalence of wounds in Indonesia is 9.2%. The most common types are scuffs or bruises, accounting for 64.1%, followed by laceration wounds at 20.1%. The prevalence of wounds in Indonesia has shown a steady increase, rising from 8.4% in 2013 to 9.2% in 2018.

The Healing process goes through 3 major phases which are the inflammation, proliferation, and remodeling phases, each involving coordinated cellular and molecular activities. Nutrition plays an essential role in supporting these phases by inducing immune responses, promoting tissue regeneration, and taking care of the skin's health. While the importance of nutrition in wound healing is recognized, specific contributions of nutrients such as iron, zinc, and vitamin E need more analysis. This review investigates the effects of those nutrients on wound healing speed, enhancing their potential in order to improve outcomes for acute and chronic wounds.

REVIEW CONTENT

1. Acute Wounds

Acute wounds are injuries that break the skin's structure and disrupt its normal function. They typically follow the body's natural healing process, progressing through the usual stages of recovery as expected (Kronowitz et al, 2020). These wounds can be challenging to manage due to factors like the person's overall health, how the injury happened, where it's located on the body, and how soon treatment begins (Lee & Hansen, 2009). Effectively managing acute wound patients' requires a thorough and holistic approach that considers each wound's specific details and relies on proven, evidence-based methods (Nick et al, 2010). Acute wound infections are quite different compared to chronic wounds that involve distinct microbial behaviours, immune system responses, and clinical symptoms (Hurlow & Bowler, 2022). While systemic antibiotics are often the most used treatment for acute wound patients, they are usually overused in chronic cases, which can lead to antibiotic resistance (Hurlow & Bowler, 2022).

Emergency care providers play an important role in acute wound care, using a systematic approach and staying up to date on the best practices to create the best possible conditions for healing (Nicks et al., 2010; Lee & Hansen, 2009).

2. Phases of Wound Healing

2.1 *Hemostasis*

Hemostasis marks the initial phase of wound healing, occurring within seconds to minutes after the injury. Platelets play a crucial role in this stage and throughout the entire healing process. They not only initiate hemostasis but also release a variety of hormones, cytokines, and chemokines essential for triggering the subsequent phases of healing (Eisinger et al., 2018). During this phase, platelets, the predominant cell type, play a critical role in preventing bacterial infections. They produce various toll-like receptors (TLRs), which regulate the synthesis of antimicrobial peptides. Once sufficient clotting has occurred, the coagulation process is deactivated to prevent excessive thrombosis. Endothelial cells and smooth muscle cells, stimulated by platelet-derived growth factor (PDGF), then work to repair the damaged vessel walls (Kingslet et al, 2002).

2.2 *Inflammatory Phase*

The inflammatory phase happens when the coagulation and hemostasis phase activate the wound healing cascade, which can be divided into an early phase which occurs neutrophil recruitment and a late phase where the monocytes appear and transform. Neutrophils are recruited to the area of the wounded skin through the response of degranulated platelets, activation of the complement pathway, and the results from bacterial degradation, where which happens for around 2-5 days after the injury unless the wound gets infected. The role of neutrophils is very important for the first days after the wound occurs since they can incur phagocytosis, kill local bacteria through their protease secretion, and assist in lysing necrotizing tissue (Reinke et al 2012).

This phase involves vascular permeability, migration of plasma into injured tissue sites, and passage of blood cells. Blood leukocytes, which play a crucial role in host defense and inflammation, are found in the initial lesions of atherosclerosis in experimental animal models. Research into the inflammatory processes associated with atherosclerosis has provided significant insights into how leukocytes are recruited to these early lesions. This recruitment is a key aspect of the disease's progression and is influenced by various molecular mechanisms that have been increasingly understood through recent studies (Libby et al, 2002).

Since this is the initial process of wound healing, it is critical for the body's protection from pathogens and to remove necrotic tissue. But too much inflammation can also cause the occurrence of chronic non-healing wounds which stop the wounds from being able to pass the remodeling stage, thus delaying wound healing.

It is important to holistically understand the inflammatory microenvironment of wounds in order to control the occurrence of inflammatory reactions and inhibition, and to prevent any abnormal or excessive inflammatory reactions (Wang et al, 2022).

2.3 *Proliferation Phase*

This phase is characterized by the significant activation of macrophages, fibroblasts, endothelial cells, and keratinocytes, which are essential for regulating wound healing, angiogenesis, and matrix deposition. Twelve hours post-injury, keratinocytes become activated due to alterations in electrical gradients and mechanical tension, as well as exposure to pathogens, cytokines, growth factors, and hydrogen peroxide (Shaw et al. 2016). This activation prompts keratinocytes at the wound site to undergo a partial epithelial-mesenchymal transition, resulting in a more migratory and invasive phenotype. Keratinocytes located behind the leading edge regulate cell adhesion through PCKα-mediated modifications in desmosome adhesiveness and Eph-mediated adjustments in adherens junctions, allowing them to reorganize in alignment with the migrating epithelial sheet (Shaw et al. 2016).

Keratinocytes navigate through debris and necrotic tissue in the wound by interacting with structural proteins from the previous extracellular matrix via integrin receptors. Matrix metalloproteinases (MMPs), particularly MMP-9 and MMP-1, are crucial for facilitating keratinocyte movement as they aid in the dissociation of integrin receptors. The breakdown of the provisional fibrin-rich wound bed generates various proteases, such as plasmin, which further support keratinocyte displacement (Rousselle et al., 2019). When keratinocytes from opposing edges meet, migration ceases due to an unidentified mechanism, leading to the formation of a narrow epithelial layer where keratinocytes establish new connections with the underlying matrix. Subsequently, keratinocytes completely reform the basement membrane and undergo terminal differentiation, allowing for the stratification and regeneration of the epidermis (Snyder et al., 2016). This Phase involves many cell types, which include vascular cells, immune cells, and fibroblasts (Jimi et al, 2021). MicroRNAs (miRNAs) are crucial in regulating the proliferation phase of wound healing, presenting opportunities for new therapeutic approaches for chronic wounds (Soliman et al., 2018). Recent studies have concentrated on the proliferation of monocytes and macrophages (Mo/Mφ) during wound healing. Research indicates that Ly6C+ Mo/Mφ proliferates in response to skin wounds, with diabetic mice showing higher proliferation rates compared to their non-diabetic counterparts (Pang & Koh, 2021). The CCL2/CCR2 signaling pathway has been identified as a significant regulator of Mo/Mφ proliferation in the wound environment, contributing to their sustained accumulation and inflammation in diabetic wound healing (Pang & Koh, 2021). These insights enhance our understanding of the cellular and molecular mechanisms involved in wound healing and highlight potential targets for improving healing outcomes.

2.4 *Remodeling Phase*

Fibroblasts are the key cells involved in extracellular matrix (ECM) remodeling. They replace the initial fibrin clots with substances such as hyaluronan, proteoglycans, and fibronectin, and later produce mature collagen fibrils during the maturation phase. In healthy, uninjured adult skin, collagen type I makes up approximately 80%, while collagen type III accounts for about 10%. In contrast, granulation tissue primarily consists of embryonic collagen type III, which comprises around 30%, with only about 10% being collagen type I (Cialdai et al., 2022).

A delicate balance is required during the sequential modifications of the extracellular matrix (ECM), which can be managed through the timely regulation of key matrix metalloproteinases (MMPs). Keratinocytes, fibroblasts, and anti-inflammatory macrophages produce collagenases that break down the helical collagen structure as part of the repair process. Another critical ECM component, elastin, must also regenerate to maintain and adapt skin elasticity. Elastin formation begins with its precursor, tropoelastin, which is evident in the early stages of healing. Fully mature elastin fibers typically emerge months after the initial injury (Diller et al, 2022).

3. Effects of Certain Nutrition for Wound Healing

3.1 *Effects of Iron Towards Acute Wound Healing*

Iron is a pivotal cofactor for enzymes and proteins which play a role in energy metabolism, DNA synthesis, respiration, apoptosis, and cell cycle arrest (Weiss et al, 2009). Iron within the skin may vary based on age, whereas in the normal dermis, iron levels tend to increase during the aging process (Levaque et al, 2003). Moreover, proteins with iron contents have a specific function which is to metabolize collagen by procollagen-proline dioxygenase (Polefka et al, 2012). Even though iron is important for wound repair (Wright et al, 2014), too much iron can have a negative effect. Too much iron in macrophages can cause a pro-inflammatory state, which leads to chronic inflammation and impaired wound healing (Sindrilaru et al 2011).

On the contrary, deficiency in iron can also have a negative effect on wound healing by affecting extracellular matrix remodeling and deposition. Recent studies have highlighted the promising role of iron nanoparticles in wound healing. These tiny particles not only exhibit strong antibacterial properties but also show the potential to accelerate the healing of chronic wounds, offering hope for improved treatments in challenging cases (Lu et al, 2023). Iron plays a dual role in wound healing, making it essential to maintain the right balance for effective recovery. Future treatments could focus on regulating tissue iron levels or utilizing iron-based nanoparticles to boost healing, particularly in stubborn chronic wounds (Wright et al, 2014).

3.2 Effects of Zinc Towards Acute Wound Healing

Zinc functions in many stages of wound healing since it has a significant function towards many cells surrounding the entire process of wound repair. Zinc is a cofactor for a lot of metalloenzymes that are needed for immune system function, cell proliferation, growth, and membrane repair. Pathological effects due tiIt has recently shown that the effects of zinc on platelets are mediated by protein kinase C (PKC)-mediated tyrosine phosphorylation of platelet proteins (Taylor et al, 2016). Treating platelets with exogenous zinc at millimolar concentrations triggers zinc uptake into the platelet cytosol and stimulates tyrosine phosphorylation of specific high-molecular-weight proteins within 30 minutes—a process that can be inhibited by PKC blockers. While the exact role of zinc in thrombus formation during tissue injury remains unclear, platelets are gaining recognition as active immune cells. They not only detect pathogens but also drive inflammatory responses by releasing cytokines and chemokines (Morrell et al, 2014).

Platelets have alpha granules that carry a lot of proteins and factors like chemokine (C-X-C motif) ligand 1 (CXCL1, GRO-α (growth regulated α protein), CXCL4, CXCL5 (ENA-78,epithelial-derived neutrophil-activating protein 78), CXCL7 (PPBP (Pro-Platelet basic protein), β- TG (Beta-Thromboglobulin), CTAP-III (connective tissue activating peptide III), NAP-2 (neutrophil-activating peptide-2)), CXCL8 (IL-8, interleukin-8), CXCL12 (SDF- 1α, stromal cell-derived factor-1α), Chemokine (C-C motif) ligand 2 (CCL2, MCP-1 (monocyte chemoattractant protein-1)), CCL3 (MIP-1α, macrophage inflammatory protein 1-α) and CCL5 (RANTES, regulated upon activation normal T cell expressed and secreted), factors which are able to activate and recruit innate immune cells towards the wound site (Blair et al, 2009). Studies show that zinc induces alpha-granule release (Taylor 2016), where they propose that zinc and platelets have a crucial role in initiating the inflammatory phase of wound healing.

3.3 *Effects of Vitamin E Towards Acute Wound Healing*

Recent studies show that vitamin E can possibly have a positive impact on wound healing. Topical application of this substance has been proven to significantly reduce healing time and increase wound contraction in human patients compared to control treatments (Ghorbanzadeh et al, 2019).

An animal study showed the effects of experimental treatments on the wound site where healing in the control group was significantly lower than in the treated groups. The discovery of a 7-day experimental treatment procedure showed wound contraction in tested groups after 14 days of surgery showed an 84% wound closure as opposed to the control group which only showed a 30% wound closure. Discovered mechanisms for vitamin E's wound healing contents include increased neovascularization, fibroblast proliferation, and increased production of transforming growth factor β and platelet-derived growth factor (Osman et al, 2020).

Another animal study conducted 585 mg/day vitamin E supplementation on rats by Sakai and Moriguchi (1997) discovered an increased function

of macrophages which prevent a decline in plasma concentration of vitamin E, which is correlated with aging. In human research, there are diverse results on the effects of Vitamin E supplementation. From a measurement of fasted blood samples conducted by Belisle et al (2009), it was discovered that Vitamin E supplementation had a major benefit for the elderly with initial elevated cytokine concentrations, since vitamins maintained these levels therefore increasing the body's immunity against infections. Particularly, Pallast et al (1999) discovered that 100mg/day induced a positive impact on cytokines, contrary to Belisle et al recently found no differences between a higher dose of 182 mg of vitamin E on cytokines. It is not clear from the results of these discrepancies, which limits the possible recommendations for vitamin E dosage that is beneficial for cytokines. Thus more study regarding this topic will be able to provide more definitive evidence.

CONCLUSIONS

This study highlights the pivotal role of nutrition in accelerating the wound healing process by influencing different stages, including the inflammatory, proliferative, and remodeling phases. Essential nutrients such as zinc, iron, and vitamin E have their own specific functions. Iron contributes to cellular functions and collagen synthesis but requires a delicate balance in order to avoid excessive inflammation that could lead to impaired healing. Zinc is important for all wound healing stages, specifically in immune response and tissue repair. Vitamin E, through its antioxidant properties, supports wound contraction and regeneration, though its optimal dosage is unclear. In conclusion, maintaining a balanced nutritional intake is crucial to enhance recovery.

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