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Review Article

Wounds: physiological mechanisms and factors affecting healing

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ABSTRACT

Wound healing involves cellular, molecular, and biochemical mechanisms that are divided into: three phases of healing: inflammatory, proliferative, and remodeling. Factors that affect wound healing are; 1. local factors, which consist of oxygenation and infection and 2. systemic factors, including: age and gender, sex hormones, stress, diabetes mellitus, obesity, drugs, alcohol and smoking and nutrition.

Keywords: Influencing factors, Healing physiology, Wounds

INTRODUCTION

The skin is the largest organ in the human body and plays an important role in various processes such as: hydration, protection from chemicals and pathogens, initiation of vitamin D synthesis, excretion and thermal regulation. Therefore, severe skin damage can be life-threatening.[1] The morphological structure of the skin consists of two layers, namely the epidermis and the dermis.[2] The epidermis is the outermost layer of the skin and is divided into four or five sub-layers, depending on the region of the body.[2] The types of cells that make up the epidermis are by far the principal cells, keratinocytes, as well as melanocytes, Langerhans cells, and Merkel cells. The dermis is a layer of connective tissue that supports the epidermis, formed by extracellular matrix proteins (collagen, elastin, proteoglycans, and glycosaminoglycans) synthesized by fibroblasts.[3] If there is a disturbance in the skin layer, the organism initiates a wound healing process to regenerate the injured area, which involves cellular, molecular, and biochemical mechanisms that are divided into: three phases of healing: inflammatory, proliferative, and remodeling.[4] This review, discusses the physiological mechanisms of wound healing, the risk factors that influence wound healing.

PHYSIOLOGICAL MECHANISMS OF WOUND HEALING

Wound healing physiology is a complex process, interrelated and overlapping, both mechanisms of cell migration and proliferation, extracellular matrix synthesis, growth factors and cytokines that coordinate the healing process. The wound healing process can be divided into three phases: inflammatory, proliferative, and remodeling.[5]

Inflammatory phase

The inflammatory reaction is characterized by sequential infiltration of neutrophils, macrophages and lymphocytes. The function of neutrophils is to clear microbes and cellular debris in the wound, although these cells produce substances such as proteases and reactive oxygen species (ROS), which can cause some damage. Macrophages have an important role in wound healing. At the initial wound, macrophages release cytokines that trigger an inflammatory response by attracting and activating leukocytes. Macrophages are also responsible for promoting and eliminating apoptotic cells (including neutrophils), thus providing a resolution to inflammation. Apoptotic cells perform phenotypic transitions to

improve conditions that stimulate keratinocytes, fibroblasts and angiogenesis to promote tissue regeneration. Macrophages promote the transition towards the proliferative phase of the healing phase. T lymphocytes migrate into the wound following inflammatory cells and macrophages peaking during the late proliferative or early remodeling phase.[6]

T lymphocytes appeared significantly on the fifth day of injury until the seventh day. Lymphocytes affect fibroblasts by producing cytokines, such as IL-2 and fibroblast activating factor. T lymphocytes also produce interferon-γ (IFN-γ), which stimulates macrophages to secrete cytokines such as IL-1 and TNF-α. T cells have a role in chronic wound healing.[7] Some studies suggest that delayed T cell infiltration followed by a decrease in the concentration of T cells in the wound is associated with impaired wound healing, while others have reported that CD4+ cells (T helper cells) have a positive role in wound healing, whereas CD8+ cells have a positive role in wound healing. (cytotoxic-suppressor T cells) have a role in inhibiting wound healing. Studies in mice where both T cells and B cells are low, show that scar formation is reduced. In addition, gamma-delta T cells regulate many aspects of wound healing, including maintaining tissue integrity, fighting pathogens, and regulating inflammation. These cells are also called dendritic epidermal T-cells (DETC), because they have a unique dentritic morphology. Dendritic epidermal T-cells are activated by stress, damage or keratinocytes and produce fibroblast growth factor 7 (FGF-7), keratinocyte growth factors and insulin-like growth factor-1, to promote keratinocyte proliferation and cell survival. Dendritic epidermal T-cells also induce chemokines and cytokines that play a role in initiating and regulating the inflammatory response during wound healing. The balance between DETC and keratinocytes helps maintain normal skin and wound healing. Deficiency of DETC indicates delayed wound healing and decreased keratinocyte proliferation in the wound. Dendritic epidermal T-cells also induce chemokines and cytokines that play a role in initiating and regulating the inflammatory response during wound healing. The balance between DETC and keratinocytes helps maintain normal skin and wound healing. Deficiency of DETC indicates delayed wound healing and decreased keratinocyte proliferation in the wound. Dendritic epidermal T-cells also induce chemokines and cytokines that play a role in initiating and regulating the inflammatory response during wound healing. The balance between DETC and keratinocytes helps maintain normal skin and wound healing. Deficiency of DETC indicates delayed wound healing and decreased keratinocyte proliferation in the wound.[6]

Proliferative phase

This phase is characterized by intense migration and proliferation of cells and synthesis of granulation tissue, consisting of extracellular matrix, macrophages, endothelial cells, and fibroblasts.[8] Injured cells secrete FGF, VEGF, EGF (epidermal growth factor), and TGF-β1 (transforming growth factor-β1) to promote the proliferation of fibroblasts, keratinocytes, and endothelial cells. Fibroblasts also synthesize extracellular matrix compounds, including type III collagen, proteoglycans and fibronectin, to support cell migration into the wound.[5,9] Vascularization in the wound begins immediately after injury, but its activity increases in the proliferative phase, to provide the oxygen and nutrients necessary for cell migration and proliferation and the synthesis of extracellular matrix compounds. Secreted mediators such as VEGF and angiopoietin stimulate endothelial cell proliferation and restructuring of the vascular system at the wound site.[10] During the proliferative phase, re-epithelialization occurs to close the epithelial gap and restore the skin's defense function.[9,11] Keratinocytes at the wound border are stimulated by growth factors, resulting in proliferation and differentiation. This stimulus triggers loss of keratinocyte adhesion molecules, inhibits physical contact with desmosomes and hemidesmosomes, and increases the migration of these cells through the extracellular matrix.[11,12]

Final phase (Remodeling)

After proliferation and synthesis of the extracellular matrix, wound healing enters a remodeling phase. In this phase, capillary regression occurs so that the vascular density of the wound returns to normal. The most critical remodeling phase is the remodeling of the extracellular matrix to achieve a normal tissue architecture. Wounds also perform contractions mediated by contractile fibroblasts (myofibroblasts) present in the wound. The role of stem cells in wound healing and tissue regeneration, with a focus on adult stem cells such as epidermal stem cells and bone-marrow (BM)-derived cells (BMDCs). Epidermal stem cells, located in hair follicles and the basal layer of the epidermis, lift keratinocytes for migration into the wound. The two main stem cells present in the bone marrow are hematopoietic SC (HSC) and mesenchymal SC (MSC). BM-MSCs were able to differentiate into various cell types such as adipocytes, osteoblasts, chondrocytes, fibroblasts and keratinocytes. Endothelial progenitor cells (EPCs) derived from HSC are key cells in neovascularization. EPC and BM-MSC are both involved in the wound healing process. Wound-induced hypoxia, which is a trigger for mobilization of EPCs into the circulation, plays an important role in the neovascularization process.[6]

Inflammatory phase: there is hemostasis of the wound area and acute inflammation through the release of cytokines,growth factors and leukocyte migration in the area.

Proliferative phase: increased migration and proliferation of keratinocytes, fibroblasts, endothelial cells and

leukocytes in the wound. Increased synthesis of extracellular matrix components and increased angiogenesis and re-epithelialization.

Remodeling phase: remodeling of the extracellular matrix, with substitution of collagen III to collagen I. Increase in MMP activity. Transient apoptosis of endothelial cells, fibroblasts, and myofibroblasts upon injury.[13]

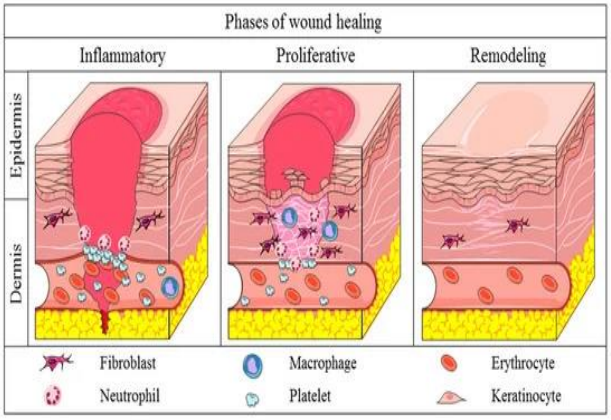

Figure 1: Physiological phases of wound healing.

FACTORS AFFECTING WOUND HEALING

Many factors affect wound healing. In general, these factors are grouped into 2 categories, namely local and systemic. Local factors are factors that directly affect the characteristics of the wound itself, while systemic factors are the disease state or health of the individual that affects the ability to heal as shown in Table 1. Some of these factors are related and systemic factors act through local effects.

Local factors

Oxygen

Oxygen is very important for cell metabolism, namely to produce energy by forming ATP and oxygen is needed for the wound healing process. Oxygen is needed to prevent wounds from infection, induce angiogenesis, increase keratinocyte differentiation, migration and re-epithelialization, increase fibroblast cell proliferation and collagen synthesis and promote wound contraction.[14,15] In addition, the production of superoxide (a key factor for oxidative killing of pathogens) by polymorphonuclear leukocytes is highly oxygen dependent. Blood vessels may be compromised and high oxygen consumption may occur due to increased metabolism, microenvironment in oxygen-deficient wounds and hypoxia. Several systemic conditions, including advanced age and diabetes, can cause vascular disturbances, resulting in poor tissue oxygenation. In the process of wound healing, poor perfusion can cause the wound to become hypoxic.[16]

Wounds with poor oxygenation will interfere with healing. Temporary hypoxia as a result of injury can trigger wound healing, but chronic and prolonged hypoxia can slow wound healing.[14,15] LIn acute wounds, hypoxia can serve as a signal that stimulates the wound healing process. Hypoxia can induce cytokines and growth factors by macrophages, keratinocytes and fibroblast cells. Cytokines produced in response to hypoxia include PDGF, TGF-β, VEGF, TNF- and endothelin-1 as well as promoter cells that are important for cell proliferation, migration, chemotaxis and angiogenesis in wound healing.[15] Adequate oxygen levels are essential for optimal wound healing. Hypoxia stimulates wound healing because it can cause the release of growth factors and angiogenesis, for that oxygen is needed to maintain the wound healing process.[14]

Infection

Local bacterial infection can occur, when the skin is injured, causing the healing process to be delayed.[17] Most of the bacteria that cause infection are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other *Streptococcal* species. In response to infection, the human organism initiates inflammatory mechanisms, with leukocyte migration and cytokine release.6 However, phagocytic activity leukocytes cause endotoxin release by bacteria, resulting in local necrosis and inflammation due to increased pro-inflammatory cytokines, higher metalloproteinase activity and decreased growth factor release.[8,18] The inflammatory response is the initial physiological mechanism of healing. The presence of chronic inflammation can inhibit the healing process, affect reepithelialization and delay wound retraction and tissue remodeling.[6,8]

Systemic factors

Age

Aging is a major risk factor for impaired wound healing. Increasing age can cause metabolic and systemic changes, the epidermis layer becomes thinner with age.[19] There are several changes in the inflammatory response of the elderly, such as delayed leukocyte migration to the area, decreased macrophage activity as phagocytosis, and decreased growth factor/cytokine release.[17,19] The elderly may also cause re-epithelialization and delayed angiogenesis, and decreased fibroblast activity and collagen remodeling.[6]

Sex hormones

Estrogen can act as an anti-inflammatory by reducing leukocyte infiltration and the release of pro-inflammatory cytokines.[20] In addition, estrogen molecules can influence the proliferation and migration of keratinocytes and endothelial cells, increasing re-epithelialization and angiogenesis in wound healing.[21] Androgen hormones (testosterone and 5α-dihydrotestosterone) have a chronic

inflammatory effect on wounds, so they can inhibit the wound healing process due to increased inflammatory cytokines and leukocyte migration.[20,21]

Stress

Stress can inhibit wound healing and various systemic diseases, through deregulation of endocrine hormones. Stress works in the nervous system and hypothalamus, so it can increase the release of the hormones epinephrine, norepinephrine, cortisol and glucocorticoids.[6,22] These molecules can induce a decrease in the release of cytokines and the immune response of leukocytes, which can cause disruption of inflammatory mechanisms and delay the wound healing process.[22]

Diabetes

Diabetes mellitus is a multifactorial systemic disease that can cause impaired wound healing. This disease affects the migration and activation of leukocytes and can increase the release of pro-inflammatory cytokines, resulting in chronic inflammation.[19] Diabetes can also affect the skin microvasculature, leading to a hypoxic environment and decreased angiogenesis. In addition, this disease can also modify the proliferation and differentiation of keratinocytes and fibroblasts, thereby delaying re-epithelialization and remodelling of the extracellular matrix.[19]

Obesity

Obesity is a chronic disease that causes several complications in wound healing. Pressure and venous ulcers associated with hematoma, edema, seroma formation and local infection are common features of obese wounds.[23,24] Cellular and molecular mechanisms associated with impaired wound healing in obesity are associated with decreased skin micro-perfusion, excessive release of pro-inflammatory cytokines, and decreased immune response.[6,23]

Drugs

There are several drugs that can inhibit wound healing, by interfering with the coagulation cascade, inflammatory mechanisms, or cell proliferation.[6] Corticosteroids which used routinely as an anti-inflammatory agent and also to modulate the immune response, but the systemic anti-inflammatory effects of steroids could induces a decrease in growth factors and cytokines, so that it can modulate healing mechanisms wound, and decreased fibroblast proliferation.[25] Non-steroidal anti-inflammatory drugs (NSAIDs) which used systemically to treat inflammation and pain, also demonstrated a negative impact on wound healing by put it down fibroblast proliferation, wound retraction and men slow down angiogenesis. When administered topically, NSAID formulations could promote wound healing and reduce local pain.[4,26] Chemotherapy drugs toocan hinder wound healing due to the mechanism of action of the molecules could reduce metabolism and cell proliferation. This results in decreased re-epithelialization, angiogenesis, collagen synthesis, and delayed wound retraction.[25] Insulin is indicated to improve diabetic ulcer healing, by increasing angiogenesis and accelerates re-epithelialization.[27-30] Metformin can improve vascular function, reduce the risk of vascular complications and accelerate epithelialization in rat diabetic ulcer models.[31] Glibenclamide can accelerate epithelialization, promote the formation of granulation tissue, and increased angiogenesis in diabetic ulcer model mice.[32,33]

Alcohol

Chronic or acute alcohol intake contributes to impaired wound healing.[6] One of the mechanisms that play a role is suppression of host immunity and increased susceptibility to infection. Studies reveal the effect of alcohol at the beginning of inflammation is a decrease in recruitment/activity of neutrophils and pro-inflammatory cytokines, then an increase in cytokines and leukocytes at a later stage of healing.[24] In addition, alcohol consumption has an influence on the proliferative phase, decreasing angiogenesis in the wound area through the expression of VEGF receptors.[6,24] As a result, a hypoxic environment occurs in the wound area with the formation of oxidative stress molecules and free radicals. Alcohol intake also impairs remodeling mechanisms, decreases collagen synthesis and alters extracellular matrix metalloproteinase concentrations.[6]

Smoke

Smoking can be associated with an increased risk of several diseases, including impaired wound healing. Studies also show that the compounds contained in tobacco cigarettes are: nicotine, carbon monoxide, and hydrogen cyanide, which can affect wound healing mechanisms.[34] Hypoxia is one of the main mechanisms associated with smoking, so it can impair wound healing, decrease erythrocyte proliferation, oxygenation, blood flow, and angiogenesis in injured tissues.[6] Smoking also increases platelet aggregation and adhesiveness, increases blood viscosity, and increases the risk of thrombosis and embolism. Furthermore, cigarette compounds can also cause a decrease in fibroblast migration, proliferation and collagen remodeling.[6,24] Smoking has an effect on the immune system, reducing neutrophil, macrophage, and lymphocyte activity, so the risk of infection is higher.[6,34]

Nutrition

Nutrition is an important factor that can affect wound healing. Wound healing requires a lot of protein, carbohydrates, fatty acids, vitamins, and minerals for the regenerative process.[19] Malnutrition can inhibit wound healing by prolonging inflammation, decreasing angiogenesis, phagocytosis and fibroblasts. metabolism, and prolongs extracellular matrix remodeling.[17] Some of

the essential nutrients for wound healing are omega-3 fatty acids (modulation of arachidonic acid pathway and cell membrane synthesis), vitamin A (increases keratinocyte proliferation), vitamin C, and carbohydrates (responsible for collagen synthesis).[19,17] Proteins and amino acids such as arginine, cysteine, methionine, and glutamine modulate immune cell activity and control collagen synthesis. Zinc is a cofactor for the biosynthesis of RNA and DNA, which plays an important role in the proliferation of wound cells.[35] Iron acts as a cofactor in collagen synthesis and if deficient it can interfere with extracellular matrix remodelling. In addition, iron as part of the hemoglobin molecule has an important role in oxygen transport and hypoxia.[19,35]

Table 1: Factors affecting wound healing.[6]

Local factors	Systemic factor
Oxygen	Age
Infection	sex hormones
	Stress
	Diabetes Mellitus
	Obesity
	Drugs
	Alcohol and smoking
	Nutrition

CONCLUSION

Wound healing physiology can be divided into three phases: inflammatory, proliferative, and remodelling. Factors that affect wound healing, 1. local factors, which consist of oxygenation and infection and 2. systemic factors, including: age and gender, sex hormones, stress, diabetes mellitus, obesity, drugs, alcohol and smoking and nutrition.

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