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WHY WOUND FAILS TO HEAL?

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ABSTRACT

Wound healing process is an orchestrated sequence of four overlapping stages namely Haemostasis, Inflammatory phase, Proliferative phase and Remodelling phase. In every phase of wound healing, certain types of cells and mediators are involved to restore the normal tissue function. Also, for proper healing of wound these phases need to function in sequential way with the availability of all components required for wound healing. But there may be some factors which may result in delaying the wound healing process. This article narrates a concise report on factors causing the delayed wound healing.

INTRODUCTION

The purpose of wound healing is to restore the normal tissue function and the first step in the healing process is haemostasis. Along with vasoconstriction, damage in tissue tend to release tissue factors and stimuli like exposed collagen, which activate coagulation pathway that leads to the production of fibrin and circulating platelet accumulation which in turn releases various growth factors (e.g., epidermal growth factor, platelets derived growth factor) and adhesion factors (e.g., thrombospondin, fibromodulin, fibronectin) therefore generating complete thrombus formation.[1]

Simultaneously, at the injury site innate immune cells initiate an inflammatory response which includes mast cells, macrophages and some specialized T-lymphocytes. They stand at ready to respond quickly to tissue damage. Also, keratinocytes immediately produce many proinflammatory mediators (e.g., Interleukin-1, Interleukin-6, Interleukin-12, Tumour necrosing factor- α). As a result of this rapid action in response to injury their happens many

vascular changes isncluding vasodilation, endothelial cell activation and increased vascular permeability. Neutrophils are the first leukocytes to be recruited to injured site. In contaminated wound, microbial products may also work as a chemoattractant for leukocytes. After a day, monocytes enter the wound and differentiate into mature macrophages and become the most abundant leukocytes at this stage. Macrophages generate several growth factors (e.g., platelet derived growth factor, insulin like growth factor 1, vascular endothelial growth factor, transforming growth factor -β1) that stimulate cell proliferation and protein synthesis. Along with it, macrophages also ingest the apoptotic neutrophils and their products. Mast cell also increased in density in the wound bed, with most of the infiltration originating from the adjacent tissue. With the increased in leukocytes density within wound, there is increase in the production of large amount of cytokine and chemoattractant resulting in enhancement of inflammatory response.[2]

Inflammation starts slowly to retard within 3 -4 days and provisional matrix begin to replace by characteristic organ of tissue repair granulation tissue, which is highly cellular, vascularized mixture of fibroblast, endothelial cell and macrophages that advance to a more permanent extracellular matrix that provide a greater mechanical integrity to wound site. During formation of granulation tissue, fibroplasia and angiogenesis are the two main processes that occurs. Simultaneously with granulation tissue formation in superficial wound there is reformation of an intact epithelial sheet.[3]

Angiogenesis is the formation of a rich capillary bed to supply the rapidly growing extracellular matrix with adequate nutrition supply to rapidly proliferating cells within healing wounds to promote granulation. During proliferation phase, capillary growth take place up to three times that of uninjured normal tissue for neovascularization with the stimulation of some proangiogenic factors (e.g., fibroblast growth factor-2 and vascular endothelial growth factor). Vascular endothelial growth factor is a potent angiogenic factor that is capable of stimulating endothelial cell migration and activation with angiogenesis.[4]

The last stage of wound healing involves the scar formation in which loosely woven, highly cellular granulation tissue gradually transforms into collagen rich and less vascularized extracellular matrix. There is also reduction in capillary diameter and density of randomly oriented collagen tissue which later changes to perpendicularly oriented collagen tissue. Along with it, fibroblast and the more specialized myofibroblast which contain contractile

protein within them will act through integrin receptors to pull on the extracellular matrix and draw the margin of wound towards one another. During wound healing, there is intense change in various components of the system as the area transforms from a weak but highly efficient formed fibrin clot into a strong scar tissue. This remodelling phase is accomplished by highly controlled expression of above-mentioned components of cellular matrix.[5]

At times, various factors interrupt this normal healing process resulting in delayed wound healing.

In general, causes of delay in wound healing can be broadly discussed under local and general aspects. Local causes are those which directly influence the factors of wound healing whereas general causes are the overall health or disease state of the individual that affect ability of wound to heal. Local factors include absence of rest to wounded part, presence of foreign body, improper oxygenation, infection, venous insufficiency, repeated trauma due to repeatedly rough dressing or using of irritating drug for dressing, etc.

General factors include age and gender, stress, ischemia, diseases (diabetes, keloids, fibrosis, hereditary healing disorders, jaundice, etc.), obesity, medications (glucocorticoid steroids, non-steroidal anti-inflammatory drugs, etc), chemotherapy, alcoholism, smoking, some immunocompromised conditions (like cancer, radiation therapy, AIDS), malnutrition, etc. [6]

Local factors

1. Absence of rest to wound

Due to movements, the delicate capillary loops of granulation tissue and the delicate epithelium are damaged. Frequent change of dressing also has the same adverse effect on wound healing.

2. Presence of foreign body

During the evaluation of wound, identification of foreign body must be done carefully as it may result in patient discomfort and delayed wound healing as its presence results in tissue reaction and inflammation**.**

3. Oxygenation

Oxygen is important for cell metabolism, especially energy production, and is critical for nearly all wound-healing processes. It prevents wounds from infection, induces angiogenesis, increases keratinocyte differentiation, migration, and re-epithelialization, enhances fibroblast

proliferation and collagen synthesis, and promotes wound contraction. In addition, the level of superoxide production (a key factor for oxidative killing pathogens) by polymorphonuclear leukocytes is critically dependent on oxygen levels. So, the proper oxygen level is crucial for optimum wound healing. But, due to vascular disruption and high oxygen consumption by metabolically active cells, the microenvironment of the early wound is depleted of oxygen and is quite hypoxic. Several systemic conditions, including advancing age and diabetes, can create impaired vascular flow, thus setting the stage for poor tissue oxygenation. As a result, there is delay in wound healing.[7]

4. Infection

Once skin is injured, micro-organisms that are normally sequestered at the skin surface obtain access to the underlying tissues. During local infection there is replication of micro-organism and the beginning of local tissue responses in the form of inflammation.

Inflammation is a normal part of the wound-healing process, and is important for the removal of contaminating micro-organisms. In the absence of effective decontamination, inflammation may be prolonged, since there is incomplete microbial clearance. Both bacteria and endotoxins can lead to the prolonged elevation of pro-inflammatory cytokines such as Interleukin-1 & Tumour Necrosis Factor - α and elongate the inflammatory phase. If this continues, the wound may enter a chronic state and fail to heal. This prolonged inflammation also leads to an increased level of matrix metalloproteases, a family of proteases that can degrade the extracellular cellular matrix. Along with the increased protease content, a decreased level of the naturally occurring protease inhibitors occurs. This shift in protease balance can cause growth factors that appears in chronic wounds to be rapidly degraded.

Also, bacteria in infected wounds occur in the form of biofilms, which are complex communities of aggregated bacteria embedded in a self-secreted extracellular polysaccharide matrix. Thus, shielding the bacteria from the phagocytic activity of invading polymorphonuclear neutrophils.[8]

Systemic factors

1. Age

Increased age is a major risk factor for impaired wound healing. Many clinical and animal studies at the cellular and molecular level have examined age-related changes and delays in wound healing. Delayed wound healing in the aged is associated with an altered

inflammatory response, including enhanced platelet aggregation, increased secretion of inflammatory mediators, delayed infiltration of macrophages and lymphocytes, impaired macrophage function, decreased secretion of growth factors, delayed re-epithelialization, delayed angiogenesis and collagen deposition, reduced collagen turnover and remodelling, and decreased wound strength.[9]

2. Stress

The Hypothalamic-Pituitary-Adrenal and the Sympathetic-Adrenal Medullary axis regulate the release of pituitary and adrenal hormones and primarily mediate the stress level in human body. These hormones include the adrenocorticotrophic hormones, cortisol and prolactin, and catecholamines (epinephrine and norepinephrine). Stress up-regulates glucocorticoids and reduces the levels of the pro-inflammatory cytokines interleukin-1β, interleukin-6, and tumour necrosis factor -α at the wound site. Stress also reduces the expression of interleukin -1α and interleukin -8 at wound sites—both chemo attractants that are necessary for the initial inflammatory phase of wound healing. Furthermore, glucocorticoids influence immune cells by suppressing differentiation and proliferation, regulating gene transcription, and reducing expression of cell adhesion molecules that are involved in immune cell trafficking. The glucocorticoids cortisol functions as an anti-inflammatory agent and modulates the T helper type-1 cells mediated immune responses that are essential for the initial phase of healing. Thus, psychological stress impairs normal cell-mediated immunity at the wound site, causing a significant delay in the healing process. [10]

3. Diabetes

Diabetic individuals exhibit a documented impairment in the healing of acute wounds. Moreover, they are prone to develop chronic non-healing diabetic foot ulcers, which are estimated to occur in 15% of all persons with diabetes. Diabetic foot ulcers, like venous stasis disease and pressure-related chronic non-healing wounds, are always accompanied by hypoxia.

A situation of prolonged hypoxia is derived from both insufficient perfusion and insufficient angiogenesis and is detrimental for wound healing. Hypoxia can amplify the early inflammatory response, thereby prolonging injury by increasing the levels of oxygen radicals. Hyperglycaemia can also add to the oxidative stress when the production of reactive oxygen species exceeds the anti-oxidant capacity. The formation of advanced glycation end-products under hyperglycaemia and the interaction with their receptors are associated with impaired

wound healing. High levels of metalloproteases are a feature of diabetic foot ulcers, and the metalloproteases levels in chronic wound fluid are almost 60 times higher than those in acute wounds. This increased protease activity supports tissue destruction and inhibits normal repair processes. Several dysregulated cellular functions are involved in diabetic wounds, such as defective T-cell immunity, defects in leukocyte chemotaxis, phagocytosis, and bactericidal capacity, and dysfunctions of fibroblasts and epidermal cells. These defects are responsible for inadequate bacterial clearance and delayed or impaired repair in individuals with diabetes.

The neuropathy that occurs in diabetic individuals probably also contributes to impaired wound healing. Neuropeptides such as nerve growth factor, substance P, and calcitonin gene-related peptide are relevant to wound healing, because they promote cell chemotaxis, induce growth factor production, and stimulate the proliferation of cells. A decrease in neuropeptides has been associated with diabetic foot ulcers formation. In addition, sensory nerves play a role in modulating immune defence mechanisms, with denervated skin exhibiting reduced leukocyte infiltration.

As a result, the impaired healing that occurs in individuals with diabetes involves hypoxia, dysfunction in fibroblasts and epidermal cells, impaired angiogenesis and neovascularization, high levels of metalloproteases, damage from reactive oxygen species and advanced glycation end-products, decreased host immune resistance, and neuropathy.[11]

4. Medications

Many medications, such as those which interfere with clot formation or platelet function, or inflammatory responses and cell proliferation have the capacity to affect wound healing. This includes glucocorticoid steroids, non-steroidal anti-inflammatory drugs, chemotherapeutic drugs, etc.[12]

Glucocorticoid steroids

Systemic glucocorticoids, which are frequently used as anti-inflammatory agents, are well-known to inhibit wound repair *via* global anti-inflammatory effects and suppression of cellular wound responses, including fibroblast proliferation and collagen synthesis leading to incomplete granulation tissue and reduced wound contraction. It also inhibits production of hypoxia-inducible factor-1, a key transcriptional factor in healing wounds.

Non-steroidal Anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs such as ibuprofen are widely used for the treatment of inflammation and Rheumatoid Arthritis and for pain management. In animal models it has been seen that systemic use of ibuprofen has demonstrated an anti-proliferative effect on wound healing, resulting in decreased numbers of fibroblasts, weakened breaking strength, reduced wound contraction, delayed epithelialization.

Chemotherapeutic drugs

Most chemotherapeutic drugs are designed to inhibit cellular metabolism, rapid cell division, and angiogenesis and thus inhibit many of the pathways that are critical to appropriate wound repair. These medications inhibit DNA, RNA, or protein synthesis, resulting in decreased fibroplasia and neovascularization of wounds. Chemotherapeutic drugs delay cell migration into the wound, decrease early wound matrix formation, lower collagen production, impair proliferation of fibroblasts, and inhibit contraction of wounds. In addition, these agents weaken the immune functions of the patients, and thereby prevent the inflammatory phase of healing and increase the risk of wound infection. Chemotherapy induces neutropenia, anaemia, and thrombocytopenia, thus leaving wounds vulnerable to infection, causing less oxygen delivery to the wound, and also making patients vulnerable to excessive bleeding at the wound site.

5. Obesity

Obese individuals frequently face wound complications, including skin wound infection, dehiscence, hematoma and seroma formation, pressure ulcers, and venous ulcers. In particular, a higher rate of surgical site infection occurs in obese patients. Many of these complications may be a result of a relative hypoperfusion and ischemia that occurs in subcutaneous adipose tissue. Also, the increased tension on the wound edges that is frequently seen in obese patients also contributes to delayed wound dehiscence. Wound tension increases tissue pressure, reducing micro perfusion and the availability of oxygen to the wound. In addition, the difficulty or inability of obese individuals to reposition themselves further increases the risk of pressure-related injuries. Moreover, skin folds harbour micro-organisms that thrive in moist areas and contribute to infection and tissue breakdown. The friction caused by skin-on-skin contact invites ulceration. Together, these factors predispose obesity to the development of impaired wound healing. Also, obesity can

be connected to stress, anxiety, and depression, all situations which can cause an impaired immune response.[13]

6. Smoking

Smoke from Cigarette consist of various harmful components including nicotine, carbon monoxide, and hydrogen cyanide. Nicotine stimulates sympathetic nervous activity, resulting in the release of epinephrine, which causes peripheral vasoconstriction and as a result there is decrease in tissue blood perfusion. Nicotine also increases blood viscosity caused by decreasing fibrinolytic activity and enhancement of platelet adhesiveness. In addition to the effects of nicotine, carbon monoxide in cigarette smoke also causes tissue hypoxia. It has an affinity 200 times greater than that of oxygen, therefore it binds to haemoglobin more aggressively resulting in a decreased fraction of oxygenated haemoglobin in the bloodstream. Hydrogen cyanide, another well-studied component of cigarette smoke, impairs cellular oxygen metabolism, leading to compromised oxygen consumption in the tissues.

Several cell types and processes that are important to healing have been shown to be adversely affected by smoke. In the inflammatory phase, smoking causes impaired white blood cell migration, resulting in lower numbers of monocytes and macrophages in the wound site, and reduces neutrophil bactericidal activity. Lymphocyte function, cytotoxicity of natural killer cells, and production of interleukins-1 are all depressed, and macrophage-sensing of Gram-negative bacteria is inhibited. These effects result in poor wound healing and an increased risk of opportunistic wound infection. During the proliferative phase of wound healing, exposure to smoke yields decreased fibroblast migration and proliferation, reduced wound contraction, hindered epithelial regeneration, decreased extracellular matrix production, and upset in the balance of proteases. Therefore, altering the wound healing process.

Beyond these direct tissue effects, smoking increases the individual's risk for atherosclerosis and chronic obstructive pulmonary disease, two conditions that might also lower tissue oxygen tension.[14]

7. Malnutrition

According to the WHO, malnutrition refers to all forms of deficiency, excess, or imbalance in a person's intake of energy and/or nutrients.[15] Malnutrition consists of either protein-energy

malnutrition or specific vitamin and mineral deficiencies. therefore, carbohydrate, fat, protein, vitamin, and mineral metabolism all can affect the healing process.

Carbohydrates and fats are the primary source of energy in the wound-healing process. Glucose is the major source of fuel used to create the cellular ATP that provides energy for angiogenesis and deposition of the new tissues.

Protein is one of the most important nutrient factors affecting wound healing. A deficiency of protein can impair capillary formation, fibroblast proliferation, proteoglycan synthesis, collagen synthesis, and wound remodelling. It also affects the immune system, with resultant decreased leukocyte phagocytosis and increased susceptibility to infection.

Collagen is the major protein component of connective tissue and is composed primarily of glycine, proline, and hydroxyproline. Collagen synthesis requires hydroxylation of lysine and proline, and co-factors such as ferrous iron and vitamin C. Deficiencies in any of these co-factors results in impaired wound healing.

Also, Arginine is a semi-essential amino acid that is required during periods of maximal growth, severe stress, and injury. It is a precursor to proline, and hence, sufficient arginine levels are needed to support collagen deposition, angiogenesis, and wound contraction. Glutamine is also one of the most abundant amino acid in plasma which is a major source of metabolic energy for rapidly proliferating cells such as fibroblasts, lymphocytes, epithelial cells, and macrophages.

Lipids are used as nutritional support for surgical or critically ill patients to help meet energy demands and provide essential building blocks for wound healing and tissue repair. They have been reported to affect pro-inflammatory cytokine production, cell metabolism, gene expression, and angiogenesis in wound sites.

Vitamins C, A, and E show potent anti-oxidant and anti-inflammatory effects. Vitamin C has many roles in wound healing, and a deficiency in this vitamin has multiple effects on tissue repair. Vitamin C deficiencies result in impaired healing, and have been linked to decreased collagen synthesis and fibroblast proliferation, decreased angiogenesis, and increased capillary fragility. Also, vitamin C deficiency leads to an impaired immune response and increased susceptibility to wound infection.

Similarly, vitamin A deficiency leads to impaired wound healing. The biological properties of vitamin A include anti-oxidant activity, increased fibroblast proliferation, modulation of cellular differentiation and proliferation, increased collagen and hyaluronate synthesis, and decreased metalloproteases mediated extracellular matrix degradation.

Vitamin E, an anti-oxidant, maintains and stabilizes cellular membrane integrity by providing protection against destruction by oxidation. Vitamin E also has anti-inflammatory properties and has been suggested to have a role in decreasing excess scar formation in chronic wounds.

Micronutrients also shown to be important for optimal repair of wound. Magnesium functions as a co-factor for many enzymes involved in protein and collagen synthesis, while copper is a required co-factor for cytochrome oxidase, for cytosolic anti-oxidant superoxide dismutase, and for the optimal cross-linking of collagen. Zinc is a co-factor for both RNA and DNA polymerase, and a zinc deficiency causes a significant impairment in wound healing. Iron is required for the hydroxylation of proline and lysine, and, as a result, severe iron deficiency can result in impaired collagen production.[16]

CONCLUSION

Wound healing process is very systematic but complex form of cell interaction with ultimate motto to restore the lost integrity of tissues. As a result of above mentioned local and general factors, healing is markedly delayed, as there is persistent inflammatory reaction or there is reduced signalling and responsiveness towards the targeted tissue. Therefore, a precise understanding of these factors makes us to distinguish or identify the factor which may be responsible for the delay in wound healing. If wound healing does not progress normally, a chronic wound may result, which is a significant menace for both, the patient as well as medical system. Thus, meticulous care is required for management of wounds.

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