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An Overview on Underlying Concepts and Mechanisms of Wound Healing

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Introduction:

The etiology, anatomical position, whether the wound is acute or chronic1, the form of healing, the presenting signs, or even the presence of the prevailing tissue types in the wound bed can all be used to characterize a wound. Both meanings play an important role in the evaluation and treatment of the wound, from symptom resolution to recovery, if possible.

A wound is defined as a deterioration of the skin's defensive function; the loss of epithelial cohesion, with or without loss of underlying connective tissue (i.e. muscle, bone, nerves)2 as a result of damage to the skin or underlying tissues/ organs caused by surgery, a blast, a slash, chemicals, heat/ cold, friction/ shear force, pain, or disease, such as leg ulcers/carcinomas[3].

Wounds heal in one of two ways: primary intention or secondary intention, depending on whether the wound should be sutured closed or left to heal spontaneously, with the development of connective tissue and regrowth of epithelium4 repairing weakened tissue.

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1. Structural organization and Functions of Skin

The integument, or skin, is the body's largest organ, accounting for 16 % of its weight and covering an area of 1.8m2. It serves many purposes, the most important of which is to provide a physical barrier to the atmosphere, enabling and restricting the inward and outward flow of water, electrolytes, and other substances while providing protection against microorganisms, ultraviolet radiation, and other harmful substances.

The epidermis, dermis, and subcutis are the three structural structures of the skin. Skin derivatives include hair, nails, sebaceous, sweat, and apocrine glands. The outer layers of the skin are constantly shed and replaced by inner cells coming up to the surface, making the skin a complex organ in continual flux. Skin thickness varies according to anatomical location, while being structurally similar across the body [1]. The skin is formed by the collision of two embryological elements: the prospective epidermis, which emerges from a surface region of the early gastrula, and the prospective mesoderm, which comes into contact with the epidermis' inner surface during gastrulation [2].

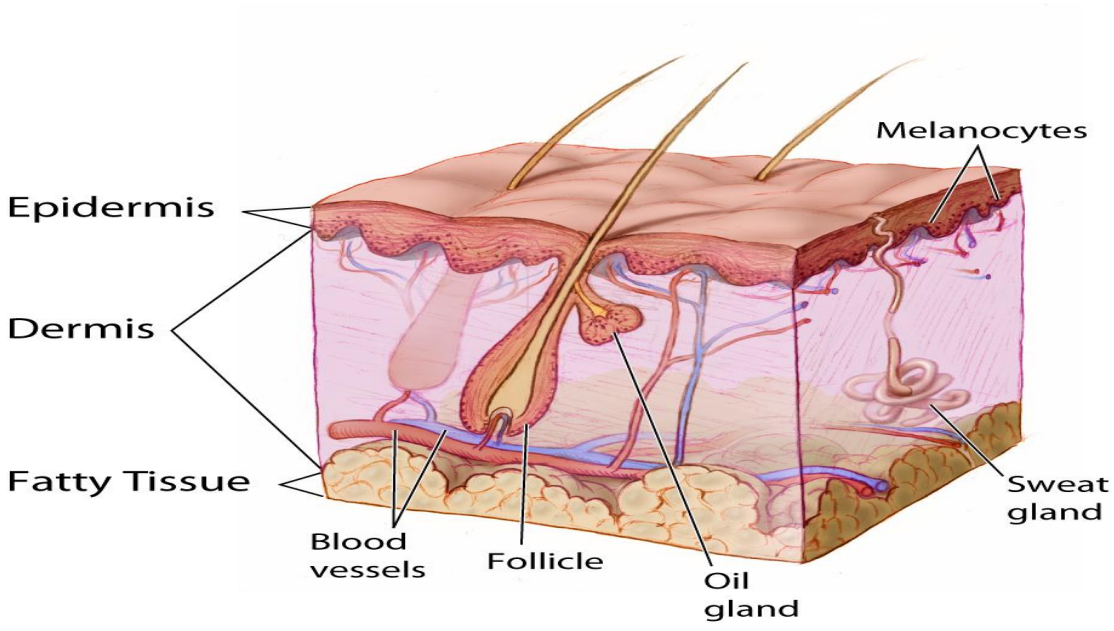

Fig 1. Structure of Skin

2. Functions of the Skin

The skin has six major functions. They are protection, thermoregulation, elimination of waste products, synthesis of Vitamin D, sensation and communication.

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2.1.1 Protection – the epidermis acts as a barrier to protect underlying tissue from mechanical injury, dehydration and the effects of harmful substances. It also prevents many disease causing organisms from entering the body.

2.1.2 Thermoregulation - capillaries in the dermis dilate and constrict in response to heat and cold. This process results in increased or decreased blood flow to the skin leading to a greater or lesser loss of body heat.

2.1.3 Elimination of Waste Products (Excretion) - cellular waste products are excreted via the sweat glands.

2.1.4 Synthesis of Vitamin D - Vitamin D is synthesized by the skin in the presence of ultraviolet radiation from the sun.

3. Wound

Wounds may be considered as physical injuries which result to rupturing or breaking of skin. The wounds are of various types of which categorizes into mild, moderate and fatal. There is an impairment of wound healing in diabetes with infection Diabetes or hyperglycemia. It is the major problem to chronic stage of wound healing? The diabetic patients associated with ulceration which becomes susceptible to major complications like infection and elimination. In traditional system of medicine, most of plants are used for therapy of different diseases and pathological conditions in the body. In the busy and fast human life, an extreme increase in chronic diseases like diabetes has also been determined. When patients those have infected wound then they face a noteworthy problem. The plants and traditional medicine are used for the therapy of infected wound and diabetes. A list of plants was claimed to use in the treatment of diabetes and wounds and has been proved while they were not scientifically proved **[2]**.

3.1 Types of Wounds:

The wounds are categorized on the basis of the cause of wound generation like open and closed wounds while on the basis of physiology of wound healing, they include acute and chronic wounds

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Three types of wound in the following box of the wound are discussed-

General Wound	Closed Wound
1. Open Wound2. Incised Wound	1. Contusions or bruises
3. Superficial Wound4. Tears Wound	2. Hematomas or blood tumor
5. Puncture Wound6. Gunshot Wound	**Crush injury**
7. Penetration Wound	1. Acute Wound
	2. Chronic Wound

3.1.1 General Wound

3.1.1.1 Open Wound:

Though an open wound blood escapes the body and bleeding is clearly visible. Open wound is further classified ii various types according to the object that occur the wound **[4]**

3.1.1.2 Incised Wound:

It is an injury with no tissue loss and minimal tissue damage. It is caused by a sharp object such as knife. Bleeding in such cases can be profuse, so immediate action should be taken.

3.1.1.3 Incised Wound:

It is an injury with no tissue loss and minimal tissue damage. It is caused by a sharp object such as knife. Bleeding in such cases can be profuse, so immediate action should be taken.

3.1.1.4 Superficial Wounds:

It is caused by sliding fall onto a rough surface. During abrasion the topmost layer of the skin i.e. epidermis is scraped off that exposes nerve ending resulting in a painful injury. Blood loss similar to a burn can result from serious abrasions.

3.1.1.5 Tear Wounds:

Generally, trauma causes such nonsurgical injury which results to tissue damage and injury.

3.1.1.6 Puncture Wounds:

They are caused by some object puncturing the skin, such as needle or nail. Chances of injection in them are common because dirt can enter into the depth of wound.

3.1.1.7 Penetration Wounds:

These wounds are caused by an artefact including a knife which cause the damage to the skin.

3.1.1.8 Gunshot Wounds:

These wounds are caused by a bullet or similar object goes into the body.

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3.1.2 Closed Wound:

The blood outflow occurs from circulating system in this wound while stay within the body. It includes discolorations, Crush injury and hematomas etc **[5]**.

3.1.2.1 Hematomas:

These hematomas or blood tumors are originated due to injury in the vessel and therefore spreads in the blood to accumulate for the skin**.**

3.1.2.2 Bruises:

Such discolorations or bruises are occurred due to blunted trauma below the skin and harms tissue of skin.

3.1.3 Crush injury:

Such type of injury is occurred due to high amount of force applied to skin for long duration of time.

3.1.3.1 Acute Wounds:

This wound is a type of tissue injury which appear as an arranged and apposite process. It is from continuous changes in the repair of anatomy and functions. Acute wounds are frequently produced by cuts or incisions. They complete by wound healing within defined time **[6]**.

3.1.3.2 Chronic Wounds:

Those wounds which are failed to recover by normal healing process. Therefore, reach to pathologic inflammation in the chronic wounds by the long time to heal or persist normally. The common causes of chronic wounds include entry of foreign bodies, trauma, hypoxia, local infection, and problems like immunodeficiency malnutrition and diabetes mellitus **[7, 8]**.

4. Factor influencing Wound Healing Process:

- Improper use of drugs.
- Elderly age group.
- Diabetes and other diseases.
- Infection in wound area.
- Improper intake of diet and inadequate nutrition.
- Inadequate oxygen supply to the wound area.

Wound healing is normal biological process in the human body. Many factors can adversely affect this process and lead to improper and impaired wound healing. A thought

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understanding of these factors and their influence on wound healing is essential for better therapeutic option for wound treatment **[9]**.

4.1. Improper Diet:

Wound healing is an anabolic mechanism that necessitates the consumption of both energy and nutritive substrates. A serum albumin level of 3.5gm/dl or higher is said to be needed for proper wound healing (7). Collagen synthesis at the wound site requires protein. A condition of malnutrition can result in an insufficient amount of protein, lowering the rate of collagen synthesis and wound tensile strength or increased chance of infection **[10,11]**.

4.2. Infection around the Wound Area:

The infection in Wound is generally, a reason of impaired wound healing process. They include *Streptococcus pyrogens*, *Streptococcus aurous*, *Pseudomonas aeruginosa* and *Escherichia coli* **[12,13]**.

Role of various nutrients in wound healing process: It has been noted that the various nutrients have important role during wound healing process. The functions and deficient effects are mentioned in the table-1.

Table-1: **Functions of nutrients in wound healing process with deficiency effects**

Nutrient	**Function**	**Deficiency Effect**
Protein	• Contributes to cellular replication and cell proliferation • Maintains tissue integrity • Serves as a glycoprotein substrate • Antibody synthesis and infection tolerance • Granulation tissue formation/fibroblastic proliferation • Collagen synthesis • Some amino acids function as enzymatic cofactors in the healing process.	• Impaired immune response • Reduced skin elasticity and resiliency, rendering it more vulnerable to damage • Delayed regeneration, decreased fibroblast proliferation, and collagen synthesis • Causes hypo-albuminuria and interstitial edema, which slows nutrient exchange between cells.

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Carbohydrate	• Energy supply to tissue • Needed for white blood cell activity	• Less glucose for cellular metabolism, resulting in protein degradation for energy instead of wound healing. • Changes in the function of white blood cells
Fat	• Role in synthesis of membrane • Membrane proliferation	• Reduced tissue regeneration
Vitamin A	• Augment fibroplasia and collagen formation • Keep a healthy humoral system • Contrary to steroidal effects on lysosomal membrane	• Reduced production of collagen • Reduced capability to cause infection • Reduced capacity to respond against harmful effects of steroids
Vitamin C	• Role as cofactor in proline hydroxylation in the collagen • Increase in cellular and humoral responses	• Delayed in the recovery by altered collagen production
Thiamine	• Played a role in energy metabolism associated with cell proliferation	• Reduced metabolism of collagen and cell proliferation
Vitamin K	• Role in the formation of coagulation factors	• Incidence of hematoma, bleeding and wound distraction
Iron	• As enzyme cofactors in the metabolism of collagen	• Caused hypovolemia hypoxia and anemia
Copper, Manganese	• As enzyme cofactors in the metabolism of collagen	• Changes in the formation of collagen
Water	• Maintain the electrolyte balance, moist conditions, quick	• Destruction of the tissues, reduction in issue perfusion

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	epidermal cell migration	and volume depletion
Zinc	• As cofactor in enzyme to cause cellular proliferation • In transcription process	• Reduced production of the enzymes • Changes in cell replication

6.1 Inadequate Supply of Oxygen and Tissue Perfusion:

Sufficient blood flow and tissue perfusion is the determinant for wound healing. The anxiety, cold and extreme pain can cause local vasoconstriction and increase in the time of healing. The tobacco chewing and smoking decrease oxygen supply and issue perfusion in wound **[14,15]**.

6.2 Drugs:

Wound healing is believed to be impaired by a variety of medications. Chemotherapeutic agents, which are often used to treat cancer, are the most well-known for delaying wound healing [16]. By inhibiting collagen formation and fibroblast proliferation, systemic glucocorticoids obstruct the natural healing mechanism.

6.3 Elderly Age:

Older age has been related to a delay in wound healing. In older people, fibroblast development and function decrease, collagen formation decreases, and wound contraction slows [17].

Diabetes and Other Diseases

8.1 Prerequisites:

Diabetic patients are particularly prone to wound healing complications. In a study, wound infection rates in diabetic patients were found to be 11 percent higher than in the general population [16]. Wound healing is often delayed by acute and chronic liver diseases. Patients with a weakened immune system are more vulnerable to wound infection.

Stages in the Wound Healing Process: It has been noted that the different stages occur in wound healing process. The functions and deficient effects are mentioned in table-2.

Table-2: **Different stages in Wound Healing Process with functions**

Phase of healing	**Time post injury**	**Cells comprised in phase**	**Function or action**

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Hemostasis	Instant	Platelets	Clotting
Inflammation	Day 1–4	Neutrophils Macrophages	Phagocytosis
Proliferation (granulation and contraction)	Day 4–21	Macrophages Lymphocytes Angiocytes Neurocytes Fibroblasts Keratinocytes	Cover the wound closure and re-establish skin structure.
Remodelling	Day 21–2 years	Fibrocytes	Improve tensile strength

8. Principles of wound healing:

9.1 The Inflammatory phase:

The inflammatory phase starts immediately after the injury that usually last between 24 and 48 hrs and may persist for up to 2 weeks in some cases the inflammatory phase launches the haemostatic mechanisms to immediately stop blood loss from the wound site. As a result of the clinically recognisable cardinal sign of inflammation, rubor, calor, tumour, dolor, and functionlesea emerge. This process is distinguished by vasoconstriction and platelet aggregation to cause blood clotting, followed by vasodilation and phagocytosis to cause wound inflammation [18].

9.2 Fibroblastic phase:

The fibroblastic process of wound healing resembles the inflammatory phase which will last anywhere from 2 to 3 weeks. Granulation, contraction, and epithelialization are the three stages in this process. Fibroblasts establish a collagen bed and new capillaries during the granulation process. Glycosaminoglycans and collagen are developed by fibroblasts, which are essential for wound healing. In the third stage, epithelial tissues are established over the wound site as the wound edges draw together to reduce the defects during contraction [19].

9.3 Epithelization phase:

One of the most important components of wound healing is epithelial cell migration. Epithelial stem cells must separate from the wound's edges and drift into the wound. Dermal basal cells usually bind to each other and to the dermis's underline basal layer. Epithelial cells

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expand and spread down around the wound following mobilization. Hair follicles that have been transected often add to the number of migrating epithelial cells. Contact guidance is a process that occurs as epithelial cells migrate through a wound and following the basal lamina or fibrin deposition. It is an important factor in epithelial migration. Epithelial migration is accompanied by enhanced epithelial mytosis.

Recent research indicates that chalcone, a water-soluble heatlabile agent secreted at the wound site, is responsible for mitosis control **[20]**.

9.4 Proliferative phase:

The Proliferative Phase (which lasts between two and three weeks) involves the following: Granulation stage: Fibroblasts lay a collagen bed and fills the hole, generation of additional capillaries. Contraction stage: Wound edges draw together to mitigate defect. Epithelialization stage: Crosses moist surface cells travel about 3 cm from point of origin in all directions **[21]**.

9.5 Contraction phase:

Differentiated fibroblasts (myofibroblasts) in the granulation tissue, which contain smooth muscle actin filaments, cause wound contraction. The wound margins migrate toward the middle of the wound as these fibroblasts contract [22, 23]. Wound contraction began earlier in ponies than it did in horses, and it was even more pronounced in ponies.

Furthermore, relative to limb wounds, it was significantly more noticeable in body wounds. As a result, ponies treat second purpose wounds considerably faster than horses, and body wounds heal significantly faster than metatarsal wounds [24]. In the wounds of the ponies, histology revealed that myofibroblasts were more organized: early formed granulation tissue, the myofibroblasts were transformed into a regularly organized pattern within 2 weeks, in which the cells were orientated perpendicular to the vessels and parallel to the wound surface. This appears to be a more favorable condition for wound contraction to occur. In the horses, myofibroblast organization took much longer. No differences were found in the number of fibroblasts, the amounts of smooth muscle actin and collagen **[25]**. Further research was performed to investigate whether the differences in wound contraction between horses and ponies were caused by differences in the inherent contraction capacity of fibroblasts or the local environment of the fibroblasts. It was found that no differences existed in the inherent contraction capacity of fibroblasts fromponies and horses in vitro **[26]**. However, the level of Transforming Growth Factor, the most important instigator of wound contraction, was significantly higher in the granulation tissue of pony wounds compared with horse wounds.

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9.6 Remodeling phase:

This phase last for 3 weeks to 2 years. New collagen is formed in this phase. Tissue tensile strength is increased due to intermolecular cross-linking of collagen via Vitamin-C dependent hydroxylation. The scar flattens and scar tissues become 80% as strong as the original [27,28]. The wound healing activities of plants have since been explored in folklore. Many Ayurveda herbal plants have a very important role in the process of wound healing. Plants are more potent healers because they promote the repair mechanisms in the natural way. Extensive research has been carried out in the area of wound healing management through medicinal plants. Herbal medicines in wound management involve disinfection, debridement and providing a moist environment to encourage the establishment of the suitable environment for natural healing process [29]. During proliferation, the wound is 'rebuilt' with new granulation tissue which is comprised of collagen and extracellular matrix and into which a new network of blood vessels develop, a process known as 'angiogenesis'. Healthy granulation tissue is dependent upon the fibroblast receiving sufficient levels of oxygen and nutrients supplied by the blood vessels. Healthy granulation tissue is granular and uneven in texture; it does not bleed easily and is pink / red in color. The color and condition of the granulation tissue is often an indicator of how the wound is healing. Dark granulation tissue can be indicative of poor perfusion, ischemia and / or infection. Epithelial cells finally resurface the wound, a process known as 'epithelialization'.

9. Risk Assessment and Prevention

When a wound is discovered, fill out the Wound Assessment Record and follow the regional policies and procedures. The appraisal will give the clinician the details he or she needs to incorporate therapies. This will aid in the selection of the most suitable action. (for example, wound bed- dry- add moisture; wound -too wet – absorb exudate).

9.1 Wound Assessment:

- Reflect on the wound's condition;
- Direct the wound's appropriate intervention;
- suggest that if the wound status does not improve within a specified timeline, re-evaluate and adjust the plan;
- monitor and evaluate overall client results (progression or regression); and decide the efficacy of care.

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10.2 Wound Cleansing

Wound cleansing is the process of removing foreign particles and surface particles from a wound. Using sterile water, regular saline, or pH-balanced wound cleansers to disinfect wounds. Surface-active agents are used in industrial wound cleansers to help in the treatment of wound pollutants.

i) Whirlpool irrigation is another form of wound irrigation. Use of whirlpool on wounds is possible for those contain slough and necrotic tissue. The whirlpool should be switched off after the necrotic tissue has been eliminated because it will damage the granulation tissue.

ii) Antiseptics including Povidone-iodine, chlorhexidine, hydrogen perioxide, Dakins (javex), and acetic acid (vinegar) have been shown to affect fibroblasts when used unselectively. As a result, it is not advised to use it on a regular basis. Healing does not need the presence of a "sterile" wound. While most untreated wounds are colonized, only a small percentage of them become infected.

iii) For wound cleansing and irrigation, pressures of 8-15 psi are considered healthy and reliable. Tissue damage can be caused by pressures greater than 15 psi. An 18-20 gauge angiocath on a 30 to 60 cc syringe will be attained pressures of 8-15 psi **[30]**

10.3 Debridement

Necrotic tissue must be replaced before wound healing can begin. If you have deep Escher, purulence, infection, or a wide region of necrotic tissue, you can debride it. If the wound has stable granulation tissue but no necrotic tissue, do not debride it. A wound can be debrided in a number of ways. Autolytic, mechanical, chemical and sharp debridement are the most common processes.

10.3.1 Autolytic

Autolytic debridement is a conduct in which the body breaks down necrotic tissue using its own digestive enzymes. This is achieved by using moisture retentive dressings or hydrogel to keep wounds moist. This causes the liquefaction of devitalized tissue by body's own enzymes.

Sharp debridement is normally painless, although this approach is slower. It can be used on full-thickness wounds as well as pressure ulcers in stages III and IV that have minimal to moderate levels of exudate and necrotic tissue. In order to prevent contamination, the wound must be carefully watched.

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10.3.2 Mechanical

Physical forces, rather than chemical (enzymatic) or natural (autolytic) forces, are used to remove devitalized tissue from a wound. There are two forms of mechanical debridement:

10.3.2.1 Wet-to-Dry Dressings

i) Wet-to-dry gauze dressings dissolve necrotic tissue and accumulate minimal quantities of exudate, but they can damage healthy tissue in the wound since they are a nonselective form of debridement.

ii) Wet-to-dry gauze dressings are not recommended for debridement because they should hinder the healing process.

The removal of the adhesive dry gauze dehydrates the emerging granulation tissue and disrupts the formation of new vessels.

iii) Because these dressings are applied damp to the wound and removed dry, they can be very painful. This technique involves cutting out slough that has been entangled in the gauze's weave.

10.3.2.2 Irrigation

High-pressure irrigation and pulsatile high-pressure lavage are two traditional methods of wound irrigation. The use of a whirlpool is a third alternative. For a discussion of irrigation refer wound cleansing [31].

11 Elevation of Moist Wound Healing

The wound healing process is helped by preserving a moist wound environment. The below are some of the advantages of moist healing:

i) **Enhanced re-epithelialization rate** – Wound healing is assisted by a wound environment that is moderately hypoxic. Angiogenesis may be aided by hydrocolloid dressings. Since moist wound healing tends to resist crust forming, epithelial movement through the moist wound bed is accelerated.

ii) **Bacterial barrier –** Occlusive dressings serve as a barrier, preventing environmental microorganisms from contacting the wound.

iii) **Decreased pain –** When the dressing hydrates the wound and insulates and preserves nerve endings, local wound pain is greatly reduced in occluded wounds.

Enhanced **autolytic debridement –** Moist wound healing can help with painless wound debridement.

12 Promotion of Thermal Insulation

When the wound bed is kept warm at body temperature, wound healing is accelerated; thus, repeated dressing changes can be avoided wherever possible. The normal healing mechanism

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can be interrupted as little as possible, according to evidence-based practice. Local hypothermia will wreak havoc on the healing process as well as the immune system.

Since it induces vasoconstriction and raises hemoglobin's tendency for oxygen, this deficiency may increase the likelihood of the infection. All of these mechanisms reduce the amount of oxygen available to phagocytes. Reduced phagocytic activity and accumulation of reactive oxygen species are two effects of hypothermia on phagocytes. Humans require a body temperature of 36.4°C to 37.2°C for optimum cellular activity. The cellular response or mechanism may be disrupted or shut down if it is outside of this range. The more occlusive a dressing is, the colder the wound temperature is. Moisture vapor transmission rates (MVTRs) vary among moisture retentive dressings.

13 Defense against Wound Healing

Shear, vibration, or friction forces may cause mechanical damage to the wound. Interventions to avoid a recurrence include:

a. Appropriate positioning and transferring techniques

b. Support surfaces for pressure redistribution to minimize or confiscate pressure

c. Treating venous leg ulcers necessitates the use of compression hosiery for the remainder of one's life.

d. Regular educational reminders for diabetic clients, with a focus on:

i)proper footwear, ii) proper foot hygiene, iii) proper nail clipping, and iv) strict blood glucose, blood sugar, blood cholesterol, and triglyceride regulation.

e. avoidance of recurrence education for both clients and their caregivers.

14 Mediators Found in a Blood Clotting process:

The different roles of mediators used in the blood clotting process have been introduced. The details of mediators are given in the table-3.

Table-3: The role of different mediators in the blood clotting process.

Mediator	**Actions**
Fibrin, plasma fibronectin	Coagulation, chemo attraction, adhesion, and cell migration scaffolding
Factor XIII (fibrin-stabilizing factor)	Chemo attraction and adhesion are caused.
Circulatory growth factors	Chemo attraction, mitogenesis, and fibroplasia are regulated by them
Complement	Chemo attraction, antimicrobial function

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Cytokines, growth factors	Chemo attraction, mitogenesis, and fibroplasia are regulated by them.
Fibronectin	Platelet aggregation ligand, early matrix formation
Thromboxane A2 (via platelet COX-1)	Chemotaxis, platelet aggregation, and vasoconstriction
Serotonin	Increases vascular permeability and acts as a neutrophil chemoattractant.
Platelet factor IV	Heparin production is neutralized, and collagenase is blocked. Chemotactic for fibroblasts and monocytes occur.

15 Factor influencing wound healing

Numerous pathophysiological and metabolic factors can affect wound healing and result in a poor outcome.26 They include local causes, such as edema, ischemia, tissue hypoxia, infection, necrosis and growth factor imbalance, as well as systemic causes including metabolic disease, nutritional status and general perfusion disturbances or pre-existing illness. These factors act by altering the wound repair environment, impeding healing and turning the acute wound into a chronic one. All processes, from wound closure time, inflammatory cell influx and fibroblast migration, to collagen and extracellular matrix deposition are delayed in this situation. 22,26,29

15.1 Hepatic Failure

Decreased clotting factors, low plasma proteins, decreased bactericidal activity, and failure of glucose regulation can all contribute to soft-tissue wound failure.

15.2 Renal Failure

Acute or chronic renal impairment may require dialysis treatment. Raised levels of uremic toxins and metabolic acidosis will affect wound healing by influencing both the innate and adaptive immune systems. Hemodialysis and peritoneal dialysis are associated with increased susceptibility to infections. Down regulation of circulating neutrophils due to their repeated activation triggering by dialysis membranes has been demonstrated. Circulating reactive oxygen species are also increased as a result of dialysis membrane activation. Deficient responses of both B and T lymphocytes also are associated with renal dialysis.87

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15.3 Respiratory Failure

Adequate gaseous exchange is essential for all biological systems, including wound healing. Tissue hypoxia secondary to hypoxemia will have profoundeffects on healing at all levels. Nutrition Septic, surgical, and trauma patients in hyper metabolic states associated with the release of endogenous cytokines from activated leukocytes experience excessive protein loss in an effort to maintain normoglycemia; these patients require additional caloric input to counter a negative nitrogen balance. Such patients consume body stores of fat and protein, particularly skeletal muscle, more rapidly than patients with normal metabolism. This, together with depletion of micronutrients and immune-nutrients, has implications in immune system function and healing.88 Elevated steroid levels because of stress are intimately involved in muscle catabolism. Insulin administration may help modulate muscle protein losses in patients with severe burns.89 Growth hormone stimulates wound healing, but its effects in critical illness need further study.90Glucose is the main fuel for wound repair. Protein malnutrition and particularly deficiencies in the amino acids arginine and methionine areassociated with compromised wound healing becauseof prolonged inflammation and disruption of matrix deposition, cellular proliferation, andangiogenesis.91,92 Malnutrition is associated with decreased deposition of collagen in skin wounds.93Glutamine has been reported to enhance the actions of lymphocytes, macrophages, and, in particular, neutrophils, and may be of particular benefit in severe infection and trauma.90 Glycine has inhibitory effects on leukocytes and may have an important role in reducing inflammation-related tissue injury.9 Micronutrients such as vitamins and minerals are critically important in immune function and wound healing. Many trace metals, including manganese, magnesium, copper, calcium, and iron, are cofactors in collagen production, and deficiencies influence collagen synthesis.91Zinc influences re-epithelialization and collagendeposition.94 Zinc has also been demonstrated to greatly influence B and T lymphocyte activity, but many other nutrients, including copper, selenium, several other metals, and several vitamins, including A, B, C, and E, have been implicated in immune dysfunction.95 Vitamin C is the main vitamin associated with poor healing, because of its influence on collagen modification.91 L Arginine is required in a variety of metabolic functions, wound healing, and endothelial function. It is important in the synthesis of nitric oxide, and deficiency is linked to immune dysfunction and failure of wound repair. Maintenance of plasma osmotic pressure is dependent on adequate production of plasma proteins and is important in maintaining body water distribution and preventing soft-tissue edema. Vitamins and minerals, particularly ascorbic acid, zinc, and

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selenium, are essential for wound repair. Copper recently has been linked to the production of vascular endothelial growthfactor.12

15.4 Smoking

Clinicians have long suspected that smoking has a poisonous effect on healing wounds, especially postsurgical flaps and grafts. In 1977, Mosely and Finseth96 demonstrated the detrimental effect of smoking on healing hand wounds. Many studies have since confirmed that smoking is harmful to a healing wound. Goldminz and Bennett97 reviewed916 flaps and full-thickness grafts and found that 1-pack-per-day smokers had three times the frequency of necrosis as nonsmokers and that 2-pack-per-day smokers had necrosis six times more frequently than nonsmokers did.[97]The mechanism of these harmful effects is likely multifactorial. Nicotine is an addictive and vasoconstrictive substance that decreases proliferation of erythrocytes, macrophages, and fibroblasts. Hydrogen cyanide is inhibitory to oxidative metabolism enzymes. Carbon monoxide decreases the Plastic and Reconstructive Surgery oxygen-carrying capacity of hemoglobin by competitively inhibiting oxygen binding.98 In one study using human volunteers, subcutaneous partial pressure of oxygen decreased significantly after10 minutes of cigarette smoking. The effect lasted for almost 1 hour.99 Taken together, this triad has obvious implications for reduction of the cellular response and efficiency of the healing process. Smoking also increases platelet aggregation and blood viscosity and decreases collagen deposition and prostacyclin formation, all of which negatively affect wound healing.100 Vasoconstriction associated with smoking is not a transient phenomenon. Smoking a single cigarette may cause cutaneous vasoconstriction for up to 90 minutes; hence, a pack-a-day smoker sustains tissue hypoxia for most of each day. Smoking also affects the cosmetic appearance of wounds,101 which has serious ramifications for the smoker who desires facial cosmetic surgery.

15.5 Corticosteroids

Anti-inflammatory steroid medications globally inhibit cell growth and production.102 They are also well known to have widespread negative effects on the wound-healing process. This is seen clinically and experimentally. A decreased inflammatory infiltrate is the most obvious effect ofsteroids.103 the macrophage response to chemotactic factors is inhibited. Effective phagocytosis by polymorph nuclear neutrophils and macrophages also is decreased as a result of the stabilizing effect of steroids on lysosomes.104 Because of the lack of an appropriate initial inflammatory response, these cells do not produce the typical growth factor[105] which has been proved by experiments. The glucocorticoids inhibit the regeneration of epithelial cells. The cell proliferation is diminished in epidermal cultures by the use of hydrocortisone.

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It has been shown in cell culture that steroids produce inhibitory effect on the fibroblast genome[105,102] Corticosteroid-treated rat fibroblasts affect endoplasmic reticulum which is indicated by low-secretory state.[106] Without the appropriate deposition and maturation of collagen, there is less wound strength and wound dehiscence is likely. Vitamin A restores the inflammatory response and promotes epithelialization and the synthesis of collagen and ground substances. Vitamin A does not reverse the detrimental effects of glucocorticoids on wound contraction andinfection.107 The recommended dose of vitamin A is 25,000 IU by mouth daily preoperatively108 and for 3 days postoperatively. Vitamin A supplementation should not be given to pregnant women

16 Findings from the study:

When wound healing is sluggish in the absence of traditional clinical features of infection, the idea of essential colonization or local infection is becoming more widely recognized. The host immune response, the number of different organisms involved, and the host immune response all play a role in the progression from wound colonization to infection but also on the immune response of the host, the number of different species involved, the virulence of the pathogens, and synergistic associations between them. There's a growing body of evidence that bacteria in chronic wounds live in biofilm cultures, where they're shielded from host defenses and develop antibiotic resistance.

Conclusion:

Wound healing is a composite process has a number of factors that can delay healing process. There is developing interest in the effects of bacteria on wound healing process All chronic wounds are colonized by bacteria while some bacteria only are beneficial to the wound healing. Wound infection is injurious to wound healing, but the diagnosis and management of wound infection is debatable, and variable thoughts among clinicians.

Understanding the conditions that influence the progression from colonization to infection may aid physicians in interpreting clinical results and microbiological investigations in chronic wound patients. Understanding the physiology and relationships inside multi-species biofilms may help researchers establish more efficient wound healing and infection management methods. The beginning of such guidelines are useful to augment the clinical utility.

References

1. Montagna W, Parakkal PF. The Structure and Function of Skin, 3rd edn. New York: Academic Press, 1974.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 6714 - 6736
Received 25 April 2021; Accepted 08 May 2021.

2. Montagna W, KligmanAM, Carlisle KS. Atlas of Normal Human Skin. New York: Springer, 1992.
3. Sumitra M, Manikandana P, Suguna L. Efficacy of *Buteamonosperma*on dermal wound healing in rats. Int. J. Biochem. Cell Biol 2005; 37: 566-573.
4. Schultz G.S. Molecular Regulation of Wound healing.InAcute,Chronicwounds.Nursingmangment, Brgant, R.A,(Ed).2nd Edn.,WB Sunders publisher ,USA. 1999 :413-429.
5. Lazarus G.S, Cooper D.M, KInghton D.R, Margolis D.J, Pecoraro R.E, Rodeheaver G, Robson M.C. Defination and guidelines for assessment of wounds and evaluation of healing, Arch. Dermatol., 1998; 130: 49- 493.
6. Menke N.B, Ward K.R, Witten T.M, Bonchev D.G Diegelmann R.F. Impaired wound healing, Clin. Dermatol., 2007 ;25 : 19-25.
7. Krishnan P. The scientific study of herbal wound healing therapies: Current state of play, Curr. Anaesthesia Crit. Care 2006;17:21-27.
8. Kerstein, M.D. Factors affecting wound healing. Adv.wound care, 2007; 10:30-36.
9. Henna,J.R and J.A.Giacopelli. A review of wound healing and wound dressing products.J foot Ankle Surg. 1997; 36:2-14.
10. Albrition, J.S. Complications of wound repair.clin.Podiatr.Med.Surg., 1991; 8:773-785.
11. Rosen.J.S and J.F Cleary. Surgical mangment of wound.Clin. PodiatrMed.Surg., 1991; 8:891-907.
12. Lazaras. Defination and guidelines for assessment of wound and evulation of healing. Arch.Dermatal 1994; 130:489-493.
13. Kumar. Wound healing potential of *Cassia fistula* on infected albino rat model,Journalsurg.Res, 2006; 131:283-289.
14. Cuzzell, J.Z and Stotts. Wound caretriel and error yield to knowledge. Am.J.Nurs.1990; 90:50 63.
15. Lavan,F.B and T.K Hunt. Oxygen and Wound healing. Clin.Plastic surgery.1990;17:463-472.
16. Franz.Optimizing healing of acute wound by minimizing complications Curr.Probl.Surg. 2007; 44:691-763.
17. Sherman R.A. A new dressing design for treating pressure ulcers with maggal therapy. PlastReconstr. Surg., 1997;100: 451-456.

18. Greenhalgh D.G. Wound healing and diabetes mellitus .Cln.Plast.Surg.2003; 30:37-45.
19. Li J, Chen J, Kirsener R, Pathophysiology of acute Wound healing, Clin. Dermatol. 2007;25:9.
20. Stadelmalmann W.K, Digenis A.G, Tobin G.R. Physiology and healing dynamics of chronic cutaneous wounds, Am. J.Surg. 1998;176: 26S-38S
21. Tamara. Book of pathophysiology basis for phase of wound healing.2008;12.
22. Romanian Biotechnological Letters Bucharest University.Romanian Society of Biological Sciences Vol. 14, No. 4, 2009, pp. 4597-4605
23. Clark RAF. Biology of dermal repair. DermatolClin 1993;11:647-666.
24. Darby I, Skalli O, GabbianiG.Smooth muscle actin is transiently expressed by myofibroblasts during experimental wound healing. Lab Invest 1990;63:21-29.
25. Jacobs KA, Leach DH, Fretz PB. Comparative aspects of the healing of excisional wounds on the leg and body of horses. Vet Surg 1998;13:83-90.
26. Wilmink JM, Van weeren PR, StolkPWT,et al: Differences in second intention wound healing between horses and ponies: Histological aspects. Equine Vet J 1999;31:61-67.
27. . Wilmink JM, Nederbragt H, van Weeren PR, et al: Differences in wound contraction between horses and ponies: the in vitro contraction capacity of fibroblasts. Equine Vet J 2001;33:499- 505.
28. Madden J.W, Peacock E.E. Studies on the biology of collagen during wound healing. Rate of collagen synthesis and deposition in cutaneous wounds of the rat, Surgery, 1968;64: 288-294.
29. Prockop DJ, Kivirikko KI, Tuderman L, Guzman NA, The biosynthesis of collagen and its disorders, N.Engl. J. Med. 1979;301;13-23.
30. Purna S.K, Babu M. Collagen based dressings-a review. Burns 26, 2000;26:54-62. Bergstrom, N., Braden, B., Kemp, M., & Ruby, E. (1998). Predicting pressure ulcer risk. *Nursing Research*, 47(5), 269.
31. Braden, B. (2001). Risk assessment in pressure ulcers prevention. In D. L. Krasner, G.T.Brown, S. (2004). The Braden Scale. *Orthopedic Nursing, 23* (1), 30-38.
32. Quickfall, J. & Shields, D. (1998). Peak performance. *Nursing Times, 94* (7), 74-77.
33. Smith, L.N., Booth, N., Douglas, D., Roberts, W.R., Walker, A., Durie, M., et. al. (1995). A critique of at risk pressure sore assessment tools. *Journal of Clinical Nursing*, 4, 153-159.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 6714 - 6736
Received 25 April 2021; Accepted 08 May 2021.

34. Vanwijck R: Surgical biology of wound healing.Bull MemAcad R Med Belg 2001; 115: 175 – 184.
35. Degreef H: How to heal a wound fast. DermatolClin 1998; 16: 365 – 375.
36. Attinger CE, Janis JE, Steinberg J, et al: Clinicalapproach to wounds: debridement and woundbed preparation including the use of dressingsand wound-healing adjuvants. PlastReconstrSurg 2006: 117(7 suppl): 72S – 109S.
37. Broughton G 2nd, Janis JE, Attinger CE: Woundhealing: an overview. PlastReconstrSurg 2006;117(7 suppl): 1e-S – 32e-S.
38. Hunt TK, Hopf H, Hussain Z: Physiology ofwound healing. Adv Skin Wound Care 2000; 13:6 – 11.
39. Glat PM, Longaker MT: Wound healing. In:Grabb and Smith's Plastic Surgery, 5th edn (AstonSJ, Beasley RW, Thorne CH, eds). Philadelphia:Lippincott–Raven, 1997; pp 3 – 12.
40. Diegelmann RF, Evans MC: Wound healing: anoverview of acute, fibrotic and delayed healing.Front Biosci 2004; 1: 283 – 289.unt TK: The physiology of wound healing. Ann Emerg Med 1998; 17: 1265 – 1273.
41. Cohen, G., Haag-Weber, M., and Horl, W. H. Immunedysfunction in uremia. Kidney Int. Suppl. 62: S79, 1997.
42. Tredget, E. B., Demare, J., Chandran, G., et al. Transforminggrowth factor-beta and its effect on reepithelializationof partial-thickness ear wounds in transgenic mice. WoundRepair Regen. 13: 61, 2005.
43. Gore, D. C., Wolf, S. E., Herndon, D., et al. Relative influenceof glucose and insulin on peripheral amino acid metabolismin severely burned patients. J.P.E.N. J. Parenter.Enteral Nutr. 26: 271, 2002.
44. Wang, J., Stuehr, D., Ikeda-Saito, M., et al. Heme coordinationand structure of the catalytic site in nitric oxidesynthase. J. Biol. Chem. 268: 22255, 1993.
45. Ruberg, R. L. Role of nutrition in wound healing. Surg. Clin.North Am. 64: 705, 1984.
46. Haydock, D. A., and Hill, G. L. Impaired wound healing inurgical patients with varying degrees of malnutrition.J.P.E.N. J. Parenter. Enteral Nutr. 10: 550, 1986.
47. Fullana, F., Grande, L., Fernadez-Llamazares, J., et al. Skinprolylhydroxylase activity and wound healing. Eur. Surg. Res.25: 370, 1993.
48. Liszewski, R. F. The effect of zinc on wound healing: Acollective review. J. Am. Osteopath. Assoc. 81: 104, 1981.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 6714 - 6736
Received 25 April 2021; Accepted 08 May 2021.

49. Mora, R. J. Malnutrition: Organic and functional consequences.World J. Surg. 23: 530, 1999.
50. Mosely, L. H., and Finseth, F. Cigarette smoking: Impairmentof digital blood flow and wound healing in the hand.Hand 9: 97, 1977.
51. Goldminz, D., and Bennett, R. G. Cigarette smoking andflap and full-thickness graft necrosis. Arch. Dermatol. 127:1012, 1991.
52. Silverstein, P. Smoking and wound healing. Am. J. Med. 93:22S, 1992.
53. Jensen, J. A., Goodson, W. H., Hopf, H., et al. Cigarettesmoking decreases tissue oxygen. Arch. Surg. 126: 1131,1991.
54. Smith, J. B., and Fenske, N. A. Cutaneous manifestationsand consequences of smoking. J. Am. Acad. Dermatol. 34:717, 1996.
55. Siana, J. E., Rex, S., and Gottrup, F. The effect of cigarettesmoking on wound healing. Scand. J. Plast. Reconstr. Surg.Hand Surg. 23: 207, 1989.
56. Petratos, P. B., Felsen, D., Trierweiler, G., et al. Transforminggrowth factor-beta2 (TGF-beta2) reverses the inhibitoryeffects of fibrin sealant on cutaneous wound repair in thepig. Wound Repair Regen. 10: 252, 2002.
57. Constant, J. S., Feng, J. J., Zabel, D., et al. Lactate elicitsvascular endothelial growth factor from macrophages: Apossible alternative to hypoxia. Wound Repair Regen. 8: 353,2000.
58. Drake, D. B., and Oishi, S. N. Wound healing considerationsin chemotherapy and radiation therapy. Clin.Plast.Surg. 22: 31, 1995.
59. Cohen, G., Haag-Weber, M., and Horl, W. H. Immunedysfunction in uremia. Kidney Int. Suppl. 62: S79, 1997.
60. Tredget, E. B., Demare, J., Chandran, G., et al. Transforminggrowth factor-beta and its effect on reepithelializationof partial-thickness ear wounds in transgenic mice. WoundRepair Regen. 13: 61, 2005.
61. Gore, D. C., Wolf, S. E., Herndon, D., et al. Relative influenceof glucose and insulin on peripheral amino acid metabolismin severely burned patients. J.P.E.N. J. Parenter.Enteral Nutr. 26: 271, 2002.
62. Wang, J., Stuehr, D., Ikeda-Saito, M., et al. Heme coordinationand structure of the catalytic site in nitric oxidesynthase. J. Biol. Chem. 268: 22255, 1993.
63. Ruberg, R. L. Role of nutrition in wound healing. Surg. Clin.North Am. 64: 705, 1984.92. Haydock, D. A., and Hill, G. L. Impaired wound healing in surgical patients

with varying degrees of malnutrition.J.P.E.N. J. Parenter. Enteral Nutr. 10: 550, 1986.

64. Fullana, F., Grande, L., Fernadez-Llamazares, J., et al. Skinprolylhydroxylase activity and wound healing. Eur. Surg. Res.25: 370, 1993.
65. Liszewski, R. F. The effect of zinc on wound healing: Acollective review. J. Am. Osteopath. Assoc. 81: 104, 1981.
66. Mora, R. J. Malnutrition: Organic and functional consequences.orld J. Surg. 23: 530, 1999.
67. Mosely, L. H., and Finseth, F. Cigarette smoking: Impairmentof digital blood flow and wound healing in the hand.Hand 9: 97, 1977.
68. Goldminz, D., and Bennett, R. G. Cigarette smoking andflap and full-thickness graft necrosis. Arch. Dermatol. 127:1012, 1991.
69. Silverstein, P. Smoking and wound healing. Am. J. Med. 93:22S, 1992.
70. J. A., Goodson, W. H., Hopf, H., et al. Cigarettesmoking decreases tissue oxygen. Arch. Surg. 126: 1131,1991.
71. J. B., and Fenske, N. A. Cutaneous manifestationsand consequences of smoking. J. Am. Acad. Dermatol. 34:717, 1996.
72. Siana, J. E., Rex, S., and Gottrup, F. The effect of cigarettesmoking on wound healing. Scand. J. Plast. Reconstr. Surg.Hand Surg. 23: 207, 1989.
73. Petratos, P. B., Felsen, D., Trierweiler, G., et al. Transforminggrowth factor-beta2 (TGF-beta2) reverses the inhibitoryeffects of fibrin sealant on cutaneous wound repair in thepig. Wound Repair Regen. 10: 252, 2002.
74. Constant, J. S., Feng, J. J., Zabel, D., et al. Lactate elicitsvascular endothelial growth factor from macrophages: Apossible alternative to hypoxia. Wound Repair Regen. 8: 353,2000.
75. Drake, D. B., and Oishi, S. N. Wound healing considerationsin chemotherapy and radiation therapy. Clin.Plast. Surg. 22:31, 1995.
76. Vihersaari T. Effect of changes in inspired tension on wound metabolism. Ann Surg. 1974;179: 889-95.
77. Ehrlichman RJ, Seckel BR, Bryan DJ, Moschella CJ. Common complications of wound healing. Prevention and management. SurgClin North Am 1991;71:1323-1351.