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CHRONIC NON-HEALING WOUND – A REVIEW

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Abstract

Wound is a disruption to the normal anatomical structure and physiological function of a tissue. Wound healing is an innate, complex physiological responds, encompassing different cell types, cellular secretions at the wound milieu and from the system. Wound healing take place in a sequence of four intertwined time-dependent phases: coagulation and haemostasis phase, inflammatory phase, proliferation phase and remodelling phase. Wounds can be clinically categorized as acute and chronic-non healing according to their time frame of healing. Causes of non-healing wound can be categorized into management, host or wound factor. The correct approach to treating wounds should effectively assist the healing process. Physiological and nutritional support at a clinical level or wound management, influence repair, as their absence results in a completely failed wound healing process. Chronic wounds affect large number of middle-age to older population with millions of new cases recorded annually amounting to high cost of treatment per head. With advances in molecular biology in the past few years, clinicians have better understanding of wound healing management practices to enhance wound healing; this includes the use of growth factors, the ability to grow cells in vitro and the development of bioengineered tissue. In conclusion, most wounds can be encouraged to heal if all the contributory factors are recognised and addressed.

Keywords: Wound healing; Wound management; Tissue; Clotting factors

1.0 Introduction

A wound is defined as a damage or disruption to the normal anatomical structure and physiological function of a tissue or part of a tissue. This can range from a simple break in the epithelial integrity of the skin, or deeper, extending into subcutaneous tissue with damage to other structures such as tendons, muscles, nerves, internal organs (soft tissues) or even the bone tissue (Peña and Martins, 2024; Kalang *et al*., 2022). A completely healed wound is defined as one that has returned to its normal anatomical structure, function and appearance of the original tissue, within a reasonable period of time. This defination is yet to be perfectly achieved in must animals (Deng *et al*., 2022; Kalang *et al*., 2022). Wound healing remains a challenging clinical problem. Hence, correct and efficient wound management is essential in every sustained wound, to prevent early or late complications in

wound management, as these complications in the wound healing process are responsible for the frequent morbidity and mortality observed in patients (Cañedo-Dorantes and Cañedo-Ayala, 2019). Wound healing is viewed as the restoration of the discontinuity in the physiological and anatomical activities of a tissue. Wound healing is an innate, complex physiological responds, encompassing different cell types (blood cells, cells from the bone marrow, resident tissue cells, extracellular matrix), cellular secretions (cytokines, and other regulatory molecules) at the wound milieu and from the surrounding wound area and body systems (other tissues) (Bettle *et al*., 2024; Cañedo-Dorantes and Cañedo-Ayala, 2019; Gonzalez *et al*., 2016). It has been estimated that chronic wounds affect 120 per 100 000 people aged between 45 and 65 years and rises to 800 per 100 000 people greater than 75 years of age. In the United State of America alone an average of one million five hundred new cases are recorded annually to add up to the existing cases (Guest *et al*., 2020; Kathawala *et al*., 2019; Demidova-Rice *et al*., 2012), with average of $50,000 treatment cost per head (Almeida *et al*., 2021; Boyce, 2001). Clinicians of recent have better understanding of wound healing management practices to enhance wound healing and this has increased success rate significantly over the past few years, particularly as a result of advances in molecular biology. This includes the use of growth factors, the ability to grow cells in vitro, the use of non-adhesive treated dressing, drugs and the development of bioengineered tissue (Kalang *et al*., 2021; EWMA, 2004; Longaker *et al*., 1991). Knowledge of scar tissue formation has also increased, fundamentally to improve on aesthetic healing (Kalang *et al*., 2021; EWMA, 2004; Velnar *et al*., 2009; Longaker *et al*., 1994). The science behind wound healing and the identification of the critical components involved in the healing process have benefited tremendously from recent advances in technology such as in the use of transgenic and knock-out animal models (Velnar *et al*., 2009).

The impact of non-healing wound on maintenance of tissue architecture had been documented by various literatures (Almeida *et al*., 2021; Kathawala *et al*., 2019; Gonzalez *et al*., 2016; Velnar *et al*., 2009; Boyce, 2001). On this background, the review was presented and the following aspects are discussed:

(a) Wound healing process
(b) Classification of wounds
(c) Causes of non-healing wounds
(d) Management of non-healing wounds
(e) Advances in wound care management

The above-mentioned topics mainly covers the aim of this review which is to present the basic information about chronic non-healing wound.

2.0 Wound Healing Process

Wound healing take place in a sequence of four intertwined time-dependent phases: (i) coagulation and haemostasis phase (ii) inflammatory phase (iii) proliferation phase and (iv) remodelling phase (**Frasier *et al*., 2024;** Ataide *et al*., 2018; Velnar *et al*., 2009).

2.1 *(i). Coagulation and haemostasis phase*

Coagulation and haemostasis start immediately after injury to prevent exsanguinations, this process also introduces the inflammatory phase (Reinke and Sorg 2012). Haemeostasis involve vasospasm, vasoconstriction, platelet plug formation and activation of the coagulation system. Owing to the neuronal reflex mechanism, injured vessels constrict rapidly due to contraction of vascular smooth muscle cells in the circular muscle layer of the blood vessel (Velnar *et al*., 2009). Thromboxane A2 (TXA2) also

causes vasospasm and vasoconstriction, it is released from the endothelial tissue. It activates platelet and platelet aggregation through the thromboxane surface membrane receptors of the platlet (Zaidi and Green, 2019). The injury leads to interactions between the blood components especially the platelets with the exposed collagen and other extracellular matrix components in the injured blood vessel and tissue. This activates the coagulation cascade, which results in platelet aggregation, clot and fibrin matrix formation in order to limit blood loss (Reinke and Sorg, 2012). von Willebrand Factor (vWF) also released from the vascular endothelium, is essential in platelet adhesion and aggregation, it also act as a carrier for coagulating factor VIII These further triggers the release of clotting factors and cytokine, from platelets (Zaidi and Green, 2019; Broughton *et al*., 2006; Etulain, 2018). The two intracellular platelet granules are the alpha and dense granules. The α-granules-contain P-selectin, fibrinogen, fibronectin, factor V, factor VIII, platelet factor IV, platelet-derived growth factor and tumour growth factor-α (TGF-α) while the dense granules-contain adenosine triphosphate (ATP), adenosine diphosphate (ADP), calcium (Ca), serotonin, histamine and epinephrine (Zaidi and Green, 2019). Hence, the degranulation of platelet attracts neutrophils, macrophages, endothelial cells, fibroblasts. Thrombin which is generated from the membrane of platelet activates fibrinogen to fibrin and subsequently forming a fibrin matrix. The fibrin mesh which serves as a scaffold for the migration of inflammatory cells, entrapped the atracted cells and also stimulates their phenotypic changes (Broughton *et al*., 2006; Etulain, 2018). The entrapped cells phenotypically change to elongated due to degranulation and also to improve cell to cell contact (Zaidi and Green, 2019). Furthermore, serotonin released from platelets increases cellular migration through improving vascular permeability. Also injured endothelial and tissue immune cells release prostaglandins and cytokines that support the inflammatory course.

2.2 *(ii). Inflammatory Phase*

The humoral and cellular inflammatory phase follows next. This wound healing phase is regarded as the major difference between scar and scarless wound healing (Reinke and Sorg, 2012). The inflammatory phase aim in establishing an immune barrier against invading micro-organisms (Reinke and Sorg, 2012; Badiavas and Falanga, 2003). It is divided into an early inflammatory phase and late inflammatory phase (Gonzalez *et al*., 2016; Strbo *et al*., 2014).

2.2.1 *Early inflammatory phase*

The predominant cells are the neutrophils and macrophages. The insult of wound activates the complement cascade and initiates molecular events, leading to infiltration of the wound site by neutrophils within 36 hours of injury. Neutrophils are the initial inflammatory cells that arrive at the wound site, with maximum population at 12-24hrs, they primarily phagocytise death cells and debris. To prevent infection within the first five days of injury, neutrophiles physiologically starts the process of phagocytosis in order to destroy and remove bacteria, foreign particles and damaged tissue (Hart, 2002; Reinke and Sorg, 2012). Due to alterations in the regulation of surface adhesion molecules of neutrophiles, neutrophils become sticky and adhere to the endothelial cells in the post-capillary venules surrounded the wound area. The neutrophils roll along the surface of the endothelium being pushed forward by blood flow and integrins, secreted by endothelial cells to enhance death tissue digestion and microbial elimination (Strbo *et al*., 2014; Broughton *et al*., 2006). Once in the wound environment, neutrophils phagocytose

foreign material and releases proteolytic enzymes and oxygen-derived free radical species (Reinke and Sorg, 2012; Brouhhton *et al*., 2006). Inflammation is supported by vascular endothelial growth factor (VEGF) and nitrous oxide (NO). Fibroblast growth factor (FGF), hypoxic enviroment induces factor1 alpha these helps in vasodilatation improving vascular permeability due to histamine (Reinke and Sorg, 2012; Brouhhton *et al*., 2006). The inflammatory response stimulates an increase in adhesion molecule to allow infiltration of inflammatory cells, cytokines and also causes vasodilation, thus, increases vascular permeability to facilitate the transport of inflammatory cellsThe cell remnants and apoptotic bodies are then phagocytosed by macrophages (Strbo *et al*., 2014; Brouhhton *et al*., 2006).

2.2.2. *Late inflammatory phase*

This is characterised by the presence of the transformed monocytes, that is the macrophages (Reinke and Sorg, 2012). Furthermore, clotting factors, complement components and cytokines, as well as elastin and collagen, are part of the late inflammatory phase, which is within 48-72 hours after injury (Daniel *et al*., 2006; Hart, 2002). These secretions attract monocytes. Monocytes undergo phenotypic changes at the wound milieu to develop into tissue macrophage, this phenotypic change enhances its physiologic role, to continue the process of phagocytosis (Etulain, 2018; Koh *et al*., 2011; Hart, 2002). Macrophages plays more significant role in wound healing as they appear and peak 72hrs post injury, they also phagocytose debris, excite recruitment and activation of fibroblast, endothelial cells, they also enhance migration of inflammatory cells into the injured site, angiogenesis and synthesis of the extracellular matrix to form new tissue (Etulain, 2018; Koh and Dipietro, 2011; Hart, 2002). Obviously, the depletion of monocytes and macrophages from the wound area causes severe healing disturbances (which can be positive or negative) on the scar tissue fibrosis (Etulain, 2018; Koh *et al*., 2011; Hart, 2002). The last cells to enter the wound site in the late Inflammatory phase are the lymphocytes, these are attracted 72 hours after injury (Daniel *et al*., 2006; Hart, 2002).

2.3 ***(iii). Proliferative Phase***

The proliferative phase starts on the third day post wounding (Broughton *et al*., 2006). It is characterized by fibroblast migration and deposition of newly synthesized extracellular matrix, angiogenesis, granulation tissue formation and re-epithelialisation (Addis *et al*., 2020; Koh and Dipietro, 2011). to replace the provisional network composed of fibrin and fibronectin during haemostasis (Addis *et al*., 2020; Broughton *et al*., 2006). Hence, the wound fills-up with granular tissue. This is possible by the already existing cells at the wound site (fibroblast, endothelial cells and keratinocytes that is if the wound involves the skin) (Addis *et al*., 2020; Broughton *et al*., 2006).

2.3.1. *Fibroblast migration*

Following injury, fibroblasts in the surrounding tissue are stimulated to proliferate for the first 3 days (Addis *et al*., 2020). Once in the wound on the third day, they produce the matrix proteins hyaluronan, fibronectin, proteoglycans and type 1 and type 3 procollagen (Addis *et al*., 2020; Koh and Dipietro, 2011; Broughton *et al*., 2006). By the seventh day the matrix protein accumulates forming scaffold for cellular migration. During the process, fibroblasts phenotypically change to myofibroblast that plays significant role in approximating the wound edges (Addis *et al*., 2020).

2.3.2 *Collagen synthesis*

Collagens are synthesized by fibroblasts; they impart integrity and strength to all tissues. This protein collagen, act as a foundation for the intracellular matrix formation within the wound area for granulation tissue (Calfee and Manning, 2002; Hart, 2002). Platelet derived growth factor (PDGF) and transforming growth factor β (TGFβ) mobilises fibroblast, that enhances the production of granular tissue and more fibroblast, which proliferate to form a matrix consisting of adhesive proteins, proteoglycans, and glycosin in a black shell as well as fibrose protein such as collagen and elastin (Kathawala *et al*., 2019; Etulain, 2018; Golebiewska and Poole, 2015). These are important in the formation of new tissue during repair, matrix and granulation tissue formation. In granulation tissue formation, matrix metalloproteins are deposited and stimulated by stimulated by PDGF, TGF, FGF which are secreted by inflammatory cell like macrophages and regulated by the tissue inhibitors of metaloproteins (TIMPS) (Cañedo-Dorantes and Cañedo-Ayala, 2019; Kathawala *et al*., 2019; Etulain, 2018). As collagen synthesis increase, fibroblast population decreases with healing (Reinke and Sorg, 2012). Unwounded dermis contains 75- 80% type II and 20 25% type III collagen, whereas wound granulation tissue expresses 40% type III collagen and 60% type II (Mathew-Stener *et al*., 2021; Hart, 2012). This implies that scar tissue strength is at an average 70% of the uninjured skin (Mathew-Stener *et al*., 2021; Han and Ceilley, 2017).

2.3.3 *Angiogenesis and granulation tissue formation*

Here new vascular beds are formed for the transportation of oxygen and nutrient. This involves the renewal of the vascular system of the affected tissue to relink nutritive perfusion (Reinke and Sorg, 2012). Modelling and establishment of new blood vessels is critical in wound healing and takes place concurrently during all phases of the reparative process (Mathew-Stener *et al*., 2021). In addition to the phagocytic activities of neutrophils and macrophages, numerous angiogenic factors are secreted during the haemostatic phase to promote angiogenesis. Resident endothelial cells at the wound edges are responsive to angiogenic factors, like the angiogenin which promotes angiogenesis (Demidova-Rice *et al*., 2012; Longaker *et al*., 1994). A balance is kept by the action of inhibitory factors, such as angiostatin and steroids to prevent excessive granulation tissue formation. Note also that, the drug bevacizumab inhibits vascular endothelial growth factor (VEGF). Inhibitory and stimulatory agents act on proliferating endothelial cells, by regulating the activation of mitosis, the promotion of locomotion and the stimulation of the host cells to release endothelial growth factors (Bryden, 2015). Under hypoxic conditions, secreted molecules from the surrounding tissue, promote the proliferation and growth of endothelial cells, in a four-step process: (i) production of proteases by endothelial cells for degradation of the basal lamina in the parent vessel in order to crawl through the extracellular matrix; (ii) chemotaxis, (iii) proliferation; and (iv) remodelling and differentiation (Bryden, 2015; Broughton *et al*., 2006). Initially, there are no vascular supply in the wound centre due to injury sustained on the tissue, viable tissue, which are limited to the wound margins, are perfused by uninjured vessels, diffusing through undamaged interstitium for revascularisation. Capillary sprouts from the surrounding edges to invade wound clot and, within a few days produce a microvascular network that is composed of numerous capillaries, that are newly formed (Cañedo-Dorantes and Cañedo-Ayala, 2019; Bryden, 2015). In angiogenesis, the endothelial cells from the surrounding healthy tissue starts to proliferate to form new blood vessels (vascular sprout) which is coordinated and promoted by cytokines like tumor necrotic factor-α (TNFα), transforming growth factor-β (TGFβ) and

vascular endothelial growth factor (VEGF). The fibroblast growth factor (FGF) also plays a role in mobilises endothelial cells by enhancing the looseness and seperation of pericytes to promote mitosis. Subsequently, circular smooth muscles are also form to complete the arrangement of the new blood vessels. At the beginning, the vessels form an inner ring of circularly arranged vessels at the wound margin followed by outer radially arranged vessels supplying the inner ones. Because the design of the vessels is similar to the sun, this has also been called 'sola cutis se reficientis'(Golebiewska and Poole, 2015; Reinke and Sorg, 2012). Chemotaxis enables cells to response appropriately to surrounding stimuli, regulate cell division, cell growth, cell migration and cell differentiation. Chemotactic agents act on cell surface receptors to direct cell migration that are involved in angiogenesis during wound healing. The contributing factors act as mediators for neovascularisaton and vessel repair (Mathew-Stener *et al*., 2021; Bryden, 2015).

2.3.4 *Epithelialization*

After the provisional matrix had been formed on the wound mileu, the surrounding keratinocytes facilitates re-epithelialisation by proliferating and migrating towards the damaged tissue to re-establish the barrier function. Migration of epithelial cells starts from the wound edges, within few hours post wounding from undamaged epithelial cells (Robson *et al*., 2001a; Natarajan *et al*., 2000). Within 24 hours of injury, the keratinocytes at the wound edge phenotypically transform and progresses into the fibrin clot and into the collagen in dermis. The suprabasal keratinocytes found behind the foremost edge of the wound progresses through cell division to fill-up the wound milieu (Cañedo-Dorantes and Cañedo-Ayala, 2019). A single layer of cells initially forms over the wound defect is accompanied by a marked increase in epithelial cell mitotic activities around the wound edges (Robson *et al*., 2001; Tomic-Canic *et al*., 2018). Cells migrating across them attach to the provisional matrix below it. When the advancing epithelial cells meet, migration stops and the basement membrane starts to form (Gurtner *et al*., 2008).

2.4 ***(iv) Remodelling Phase***

As the final phase of wound healing, the remodelling phase is responsible for the development of new epithelium already formed during the proliferative phase and the final scar tissue, that is, primarily the formation of new epithelium and scar tissue. The main cells here are still the fibroblast and the modified cell, that is, myofibroblast.

(Cañedo-Dorantes and Cañedo-Ayala, 2019). Synthesis of the extracellular matrix in the proliferative and remodelling phases is initiated contemporarily with the development of granulation tissue. This phase may last up to 1 or 2 years, or sometimes for an even more prolonged period of time. Remodeling aims at balancing the matrix accumulation as well as, progressive breaking down of the matrix (Cañedo-Dorantes and Cañedo-Ayala, 2019; Tomic-Canic *et al*., 2018). Along with intracellular matrix maturation, collagen bundles increase in diameter, increase in hyaluronic acid, and degradation of fibronectin. The tensile strength of the wound increases progressively in parallel with collagen remodelling (Tomic-Canic *et al*., 2018; Natarajan *et al*., 2000). Collagen fibres may regain approximately 70-80% of the original strength compared with unwounded tissue (Robson *et al*., 2001b). Sixty percent of which is attained within 6 weeks (Abazari *et al*., 2020). Fibroblast alter the extracellular matrix that it produced, transform to myofibroblast and

later apoptosis. Myofibroblast are capable of contracting as they contain actin and myosin; this alters the matrix in the formation of scar tissue. Gradually becoming avascular and acellular scar. The acquired final strength depends on the localization of the repair and its duration, but the original strength of the tissue can never be regained (Abazari *et al*., 2020; Calfee and Manning, 2002). Synthesis and breakdown of collagen as well as extracellular matrix remodelling take place continuously and both tend to equilibrate to a steady state about 3 weeks after injury (Velnar *et al*., 2009; Hart, 2002). Matrix metalloproteinase enzymes, produced by neutrophils, macrophages and fibroblasts in the wound, are responsible for the degradation of collagen (Xue and Jackson, 2015; Robson *et al*., 2001b). Their activity is tightly regulated and synchronized by inhibitory factors, thereby, promoting the development of new matrix. Although the initial deposited collagen bundles are highly disorganised, subsequent reorganisation is done to achieve an organised collagen structure during the final stages of the remodelling phase, alongside with the wound contraction that has already begun in the proliferative phase (Abazari *et al*., 2020; Hart, 2002). The density of myofibroblasts, fibroblasts and macrophages are reduced by apoptosis (Abazari *et al*., 2020). With time, the growth of capillaries stops, blood flow to the area declines and metabolic activity at the wound site decreases. The end result is a fully matured scar with a decreased number of cells and blood vessels with high tensile strength (Hart, 2002; Velnar *et al*., 2009).

3.0 Classification of Wounds

Wounds can be classified according to various criteria. Time is an important factor in wound management. Thus, wound can be clinically categorized as acute and chronic-non healing according to their time frame of healing (Demidova-Rice *et al*., 2012; Robson *et al*., 2001b).

3.1 *Acute Wounds*

Acute wounds proceed normally by following a timely and orderly healing pathway, with the end result of both functional and anatomical restoration (Demidova-Rice *et al*., 2012; Toy, 2005; Robson *et al*., 2001b). The time course of healing usually ranges within 30 days from the day of wound insult for soft tissue (Toy, 2005).

3.2 *Chronic Wounds*

Chronic wounds are those that fail to progress through the normal stages of healing and they do not repair in an orderly and timely manner (Frasier *et al*., 2024; Toy, 2005). They are characterised by infections, excessive inflammation, and/or poor capability of cells to respond to repairs (Toy, 2005). The healing process is incomplete and disturbed by various factors, which prolong one or more stages in the wound healing process (Nastaran *et al*., 2025; Aderibigbe, 2021). Chronic wounds may result from various causes, including infection, neuropathic, pressure, arterial and venous insufficiency, burns, vasculitis and foreign body like in cutaneous sinus tracts from the lumbar, paralumbar, and caudal flank in animals which are commonly associated with peritoneal or retroperitoneal foreign bodies (FiToz *et al*., 2001; Shahrousvand *et al*., 2021). These foreign bodies at the wound site can result in chronic draining sinus tracts (Daniel and Mathieu, 2006; Kim *et al*., 2003). Making it susceptible to infection. Subsequently, the use of topical antibiotics, should be restricted to clinically infected wound. The clinical approach to chronic draining tracts and skin sinuses should be thorough (Addis *et al*., 2020; Han *et al*., 2017; Kim *et al*., 2003). A draining cutaneous tract below the medial canthus of the ipsilateral eye can be due to endodontic

conditions like the slab fracture of the maxillary fourth premolar tooth, which often results in pulp exposure and endodontic infection (Lewis, 2011; Staudte *et al*., 2004; Hale, 2001). Poorly healing wounds or draining wounds generally can be life-threatening, problematic to treat, or even zoonotic.

Other reasons for chronic wounds include high level of proteases in wound milieu, high levels of cytokines, low population of keratinocytes, endothelial cells, and fibroblasts, and high level of peroxynitrite, due to reactions between nitric oxide and hydroxyl-free radicals (Toy, 2005). Diagnostic steps include cytology, biopsy and histopathology, culture and susceptibility, biochemical, serology, and diagnostic imaging particularly when there has been surgical intervention, trauma, or history of a wound in the region, and an accurate and early diagnosis is a necessity (John, 2014; Daigle *et al*., 2001; Kim *et al*., 2003). Furthermore, prolong residing of inflammatory cells within the wound milieu produces various Reactive Oxygen Species (ROS), damaging the structural elements of the extracellular matrix, cell membranes (receptors) thereby, resulting in early cell aging and subsequently chronic wound (Demidova-Rice *et al*., 2012).

4.0 Causes of Non – Healing Wounds

Veterinarians do not witness the large number of chronic, non-healing wounds that the human counterparts attend to. Probably because, animals are largely exempt from co-morbidities that exist in humans, such as obesity, alcoholism, chronic diabetes and cardiac disease(Mathew-stener *et al*., 2021; Etulain, 2018). Many wounds that are perceived to be non-healing are in-fact simply just not provided with the right conditions in which to heal or could be due to frequent interferences by the patient. These factors should be considered when faced with a non-healing or atypical wound, it can be management, host or wound factor (Etulain, 2018; Broughton *et al*., 2006; Badiavas *et al*., 2003).

4.1 *Management Factors*

Tension: Tension at the wound site can lead to reduced blood supply and inadequate wound contraction. Wound contraction will naturally stop in the presence of tension on the wound edges. That is, the tension exceeds the pull of the myofibroblasts although the defect may still be re-epithelialised (Mathew-Stener *et al*., 2021; Han and Ceilley, 2017).

Pressure ischemia: Prolong pressure on a skin that is over a bony prominence is particularly prone to ischemia. The prolonged pressure could be due to inadequate bedding, or inappropriately bandaged wound. Ischemia leads to necrosis and development of a decubital ulcer (pressure sore) (Demidova-Rice *et al*., 2012; Scott *et al*., 2001). Relieving pressure is imperative. The usual reason for inadequate tissue oxygenation, is local vasoconstriction as a result of sympathetic over activity. This may occur because of blood volume deficit, unrelieved pain, or hypothermia, especially involving the distal extent of the extremities (Bryden, 2015; Velnar *et al*., 2009). Areas such as the axilla, inguinal area, lip commissure, footpads and skin over joints are subject to repeated shearing forces, which constantly disrupt wound healing. Furthermore, that may affect the oxygen tension at the wound milieu to lower than the 5mmHg as required at the wound site for optimal wound healing process (Han and Ceilley, 2017). Immobilization and cage rest should be instituted for animals, which have tendency to form indolent wounds (Mathew-Stener *et al*., 2021; Velnar *et al*., 2009).

Maceration: Small animal wounds are often highly exudative in the inflammatory and even early repair stages of wound healing. If a dressing is excessively occlusive, or the bandage layer is non-permeable, and wet,

then wound maceration may occur (Velnar *et al*., 2009; Kim *et al*., 2003).

Desiccation: Wounds that dry tends to easily sustain damage, disrupting the fragile migrating epithelium and capillary buds. Dressing materials such as hydrogels, which allow some moisture retention in the wound, can be used in the repair phase, once exudate production has dropped (Mathew-Stener *et al*., 2021; Daniel and Columbus, 2006b).

Self-mutilation: Animals are prone to licking or chewing at their dressings and wounds, and can cause severe disruption to wound healing. This can be prevented with padded bandages, splints side braces, Elizabethan collars and wire sutures (Mathew-Stener *et al*., 2021; Velnar *et al*., 2009).

Devitalized soft tissues: Inadequate surgical debridement of devitalized tissues is devastating for wound healing. Closing a wound over non-viable tissue and/ or detritus is a common reason for delayed healing and dehiscence (John, 2014; Velnar *et al*., 2009). Eschar: Failure to remove the hardened scab of dead tissue and dried exudate will act to impedence to contraction and may also harbour bacteria (Mathew-Stener *et al*., 2021; Velnar *et al*., 2009).

4.2 *Host Factors*

Malnutrition: Nutritional deficiencies can impair wound healing and interfere with the ability of the body to fight infection. Hypoproteinaemia less than 2g/dL will impede wound healing. Hence, supplemental feeding should be instituted in patients with a negative nitrogen balance, possibly with the addition of arginine, glutamine and DL-methionine (cysteine) (Mathew-Stener *et al*., 2021; Etulain, 2018; Velnar *et al*., 2009). So also, other trace elements such as vitamin A, C and zinc are known to enhance healing (Han and Ceilley, 2012).

Uremia: Uremic individual will take longer time to form granulation tissue due to reduce collagen deposit. Furthermore, epithelialisation will also be delayed (Mathew-Stener *et al*., 2021; Rizwanullah *et al*., 2020). Efforts to normalize azotemia or any other metabolic disorder should be instituted (Mathew-Stener *et al*., 2021; Rizwanullah *et al*., 2020).

Endocrinopathy: The absence of the adrenal, thyroid or pituitary gland does not affect wound healing but excessive administration of steroids retard wound healing process (Kursh *et al*., 1977). The neuropathic and angiopathic effects of chronic diabetes causes huge wound healing problems in people. Hypothyroid patients should also be considered as slow healers, although there are only anecdotal reports (Mathew-Stener *et al*., 2021; Bryden, 2015; Velnar *et al*., 2009).

Corticosteroid medication: Glucocorticoids, with their potent anti-inflammatory effects, will decrease the inflammatory response, slow down granulation tissue formation, and retard epithelialization. As it has being documented that, animals should be tapered off these drugs, or at least reduced down to a minimally acceptable level (Mathew-Stener *et al*., 2021; Bryden, 2015; Velnar *et al*., 2009).

Old age: It often appears that wounds in the elderly heal more slowly than in the younger patients. This has been documented in both humans and animals. It appears that a normal consequence of aging is lack of skin perfusion, fragility of skin

and increased susceptibility to infection. The impact of ischemia on wound healing is also exacerbated in the old aged. Older patients require meticulous nursing care, a high plane of nutrition, and attention must be paid to ensuring a good blood supply to the wound area (Mathew-Stener *et al*., 2021; Velnar *et al*., 2009).

4.3 *Wound Factors*

This involves basic factors like, wound size, wound dept, affected site of location (loss skin or joint), if edematous or dehydration, pressure, vascularity, infection, foreign materials others are:

Radiation therapy: This markedly delay wound-healing, and wounds in irradiated tissue can be challenging! Complications may be controlled with finer fractionation, reduced dose and a skin-Sparing source of ionizing radiation. The best option for these wounds involves, bringing in a robust blood supply from outside the irradiated zone (Mathew-Stener *et al*., 2021; Velnar *et al*., 2009). Wound healing can be seriously affected by radiotherapy (Douglas, 1957).

Chemotherapy: Surgery has several applications in cancer management and treatment and is often the initial and preferred treatment of choice for many cancers (Douglas, 1957). The effect of cytotoxic agents on traumatic wounds has not been well documented, although their mechanism of action on rapidly dividing cells would suggest them to be detrimental to wound healing (Mathew-Stener *et al*., 2021; Velnar *et al*., 2009). Chemotherapy has been demonstrated to decrease fungating wound size by destroying cancer cells, reducing pressure on nerves, blood and the lymphatics. Hence, reducing wound exudate, blood loss and enhancing cancer wound healing, but it can also lead to wound-related difficulties Nastaran *et al*., 2025; Douglas, 1957).

Neoplasia: This should always be suspected when faced with a non-healing wound. Cancerous lesions can appear erosive rather than proliferative (e.g., squamous cell carcinoma). Biopsy should be performed routinely with delayed healing or an atypical wound appearance (Mathew-Stener *et al*., 2021; Velnar *et al*., 2009).

Foreign body: Draining tracts, recurring, and partially responsive wounds are typical of a foreign body. These wounds will have granulomatous lining and a rounded epithelial edge (wound trying to heal). Discharge varies from serous to purulent. These wounds can be biopsied, cultured, radiographed, ultrasounded, contrast CT, or MRI. Due to their migratory nature, finding foreign bodies maybe challenging. Hence, exploration should be planned for a thorough and meticulous search (Mathew-Stener *et al*., 2021; Shahrousvand *et al*., 2021; Velnar *et al*., 2009).

Exposed bone: Shearing and severe degloving injuries can be slow to heal, due to the extra time taken for granulation tissue to migrate across the bone. Bone can be drilled or scraped after several days of wound management to provide a moisturizing clot, but has not been shown to promote fibroplasias (Han and Ceilley, 2012; Velnar *et al*., 2009). The pH of the wound bed is a key factor, as angiogenesis, keratinocyte, fibroblast migration and signalling it's also important in matrix metalloproteinase activity, and microbial proliferation, is favoured by an acidic environment (Douglas, 1957).

Infection: Infection has serious impact on wound healing. Aerobic and anaerobic microbial cultures should be performed, along with biopsy for histopathology especially when it involves macerated tissue. In chronic wounds the common microbes isolated include, *Staphylococcus aureus, Pseudomonas aeruginosa*, and β-hemolytic Streptococci are the primary causes of chronic wound infections, other microbes include *Enterococcus* spp,

Klebsiella pneumoniae, Acinetobacter baumanii, and Enterobacter spp. coagulase-negative Staphylococci, and *Proteus* species (Douglas, 1957). Infected wounds generally respond to aggressive open wound management and appropriate systemic antibiotic therapy. Mycobacterial infections generally require a combination of prolonged antibiotic therapy with radical surgical interventions. It is also good to note that, microbial infection by some bacteria organism like, Actinobacillus, Actinomyces and Nocardia, are generally underdiagnosed and can lead to granulomas (Mathew-Stener *et al*., 2021; Velnar *et al*., 2009).

Spider/snake bite: Envenomisation can cause severe localized necrosis and pain. In many case the victim may develop necrotic lesion which may expand up to several inches over days or weeks. Aggressive debridement and initial open wound management is indicated, to ensure the removal of all necrotic tissue. The wounds are hence rendered, reconstructed as the process enhances blood supply. Second intention wound healing may then be employed, which is likely going to take several months (Mathew-Stener *et al*., 2021; Velnar *et al*., 2009).

Management: Wound can heal by primary or secondary intensions. Primary intension involves wound edges been approximated by suturing or stable, that is, closed. Healing here is faster with minimal tissue repair, majorly with surgical wounds (Gonzalez *et al*., 2016; Damidova-Rice *et al*., 2012). Secondary intensions, where the wound edges are not apposed, hence, healing of the wound occur from the wound floor, gradually going upwards. The healing is typically by granulation tissue formation, wound contraction and re-epithelialisation. This form of healing is generally seen were there was excessive soft tissue lost due to trauma or burns. Hence, myofibroblast play major role in this type of healing (Gonzalez *et al*., 2016; Damidova-Rice *et al*., 2012).

5.0 Management of Non - Healing Wounds

The correct approach to treating wounds should effectively assist the healing process and this has an important impact on the final clinical outcome. Physiological and nutritional support at a clinical level or wound management, significantly influence repair, as absence of these (physiological and nutritional) support, often results in a completely failed wound healing process (Bryden, 2015; Natarajan *et al*., 2000; Labler *et al*., 2006). The first stage of wound management should be a thorough assessment of the wound and the patient. The process begins with diagnosis of the wound etiology and continues with optimizing the patient's medical condition, particularly blood flow to the wound arca (Kadam *et al*., 2019; Bryden, 2015; Rivera *et al*., 2007; Strecker-McGraw *et al*., 2007; Natarajan *et al*., 2000). Debridement and prevention of infection are very essential in wound management, especially in long standing (contaminated/ infected) or wounds with necrotic tissue as it accelerates wound healing (Xue and Jackson 2015; Rivera *et al*., 2007; Strecker-McGraw *et al*., 2007; Broughton *et al*., 2006). However, special tissues, such as tendons and fascia, are not removed except in severe conditions. The next important step is the wound lavage and must be employed cautiously especially where granulation tissue is present (Bryden, 2015; Strecker-McGraw *et al*., 2007). Note that, palliative wound management can be employed in wounds that lack ability to heal due to untreatable causes, as in terminal illness (such as cancer or end-stage disease). Regardless of the reasons behind a non-healing wound, the goals of care must be those of pain management and comfort (Marc *et al*., 2008).

6.0 Advances in Wound Care Management

6.1 *Platelet rich plasma (PRP)*

Platelet rich plasma therapy is being used with increased frequency to treat variety of conditions, including non-healing wounds. It works very well alongside with doses of anti-inflammatory medication and antibiotics (White, R. and Cutting, 2006; Vincent and Roger 2005; Veves *et al*., 2001; Knighton *et al*., 1986). Recently the use of PRP has gained wide acceptance especially in the management of chronic wounds. PRP has being reported to reduce inflammatory response at the wound site, prevent infection, enhance cell division and response to cytokines; and also increase cytokines concentration at the wound site (Xu *et al*.,2020; Golebiewska and Poole, 2015). It is also recommended in chronic wound management (Golebiewska and Poole, 2015).

6.2 *Cytokines*

It has been observed that, a second wound, inflicted on a previous injury, heals more rapidly due to release of more wound factors (Deng *et al*., 2022; Douglas, 1957). Novel techniques of topical growth factor application can optimize both the cellular and molecular environment, thus decreasing healing time by modifying inflammation and accelerating the proliferative phase (Lin *et al*., 2008; Sosa *et al*., 2008). Over the past two decades several recombinant growth factors has been tested for their ability to accelerate the healing of chronic wounds. Some promising results had been obtained using epidermal growth factor and keratinocyte growth factor-2 for venous ulcers, and fibroblast growth factor and platelet derived growth factor (PDGF) for pressure ulcers (Velnar *et al*., 2009; Gurtner *et al*., 2008; Longaker *et al*., 1994). It's been established that, lower levels of some cytokines maybe responsible for the chronicity of wounds like the epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor-b (TGFb), PDGF, and vascular endothelial growth factor (VEGF), interleukins (IL) 1 and 6, and tumor necrosis factor-a (TNF-a) (Han and Ceilley, 2012).

6.3 *Bioengineered skin*

A bioengineered skin is aimed at re-creating the wound arena to enhance tissue and organ regeneration (Kadam *et al*., 2019; Urciuolo *et al*., 2019). A number of bioengineered skin products or skin equivalent has become available for the treatment of acute and chronic wounds as well as burns. Since the initial use of keratinocyte sheets (Quesenberry *et al*., 2002; Vincent and Roger 2005). A bioengineered skin is expected to be biocompatible, with barrier properties, heat resistant and mechanically stable. Others qualities required include the, ability to absorb excess fluid from the wound bed, provide adequate aeration and moisture and medium for systematic delivery (for drugs like antibiotics and cytokines) (Augustine *et al*., 2014). More complex constructs have been developed and tested in human wounds. These skin equivalents may contain, living cells, such as fibroblasts or keratinocytes, or both (Strbo *et al*., 2014; Badiavas and Falanga, 2003), while others are made of acellular materials or extracts of living cells. The clinical effect of these constructs are 15-20 percent better than the conventional 'control' therapy, but there are debates over what constitutes an appropriate control (Urciuolo *et al*., 2019; Veves *et al*., 2001). Some of the bioengineered products are matrix-based platform, host cell-base platform, wound fluid-based models, infection-immunity interface platform, ex-vivo porcine skin models and ex-vivo human skin models (Kadam *et al*., 2019; Regan, 2007).

6.4 *Electrical field stimulation*:

Electrical field stimulation may optimize the remodeling phase by promoting more efficient fibroblast recruitment, collagen deposition and re-organisation (Ramelet *et al*., 2009; Sosa *et al*., 2008).

6.5 *Gene therapy*

This involves the technology to introduce certain genes into wounds by a variety of physical means (Patenall *et al*., 2024; Slama *et al*., 2001). In cancer management the prescribed "cancer driver gene" is targeted, so also, in wound healing "wound healing driver genes" are the focus (Tang *et al*., 2021; Regan, 2007). The manipulated cells are being re-introduced into the wound via simple injection or the use of a gene gun or biological vectors. The introduction of the gene rather than its product, for example a growth factor, is seen as a less expensive and potentially more efficient delivery method (Slama *et al*., 2001), prosthetic materials can favour tissue repair and gene therapy which is currently in pre-clinical development, and may be able to provide a way for selective healing stimulation (Hode, 2006; Sabolinka *et al*., 2000). Gene transfer is a direct delivery system to the wound site planned on delivering a genetic material encoding growth factors directly into the target cells. This then, could result in the protein synthesis, that can last for days (Hendrick *et al*., 2013.

6.6 *Stem cell therapy*

Pluripotential stem cells (PSCs), these are the precursors to all cells of all tissues. Specialised stem cells, are capable of differentiating into a variety of cell types (Urciuolo *et al*., 2019; Quesenberry *et al*., 2002). 66]. The application of autologous bone marrow and its cultured cells, may accelerate the healing of non-healing chronic wounds, which needs to be confirmed in a larger controlled trial (Patenall *et al*., 2024; Strbo *et al*., 2014). Currently, the majority of stem cell-based trials for wound healing are utilizing mesenchymal stem cells-based interventions, however, adipose stem cells-based interventions are also in use. There are tremendous evidence that aging and disease negatively affect stem cell function and may adversely impact the effectiveness of autologous cell therapy, particularly in the aged and diabetic. Delivery methods include at target (through site) delivery and intravenous delivery system.

7.0 Summary

Wound healing is an innate, complex physiological responds targeted at restoring tissue normalcy. Immediately after injury coagulation and haemostasis start to prevent blood lost, this response introduces the inflammatory phase. The inflammatory phase aim in establishing an immune barrier against invading micro-organisms. It is characterized by fibroblast migration and deposition of newly synthesized extracellular matrix to replace the provisional network composed of fibrin and fibronectin during haemostasis. During the process, fibroblasts phenotypically change to myofibroblast that plays significant role in approximating the wound edges. Synthesised collagen at the wound site, act as a foundation for the intracellular matrix formation within the wound area. Modelling and establishment of new blood vessels is critical in wound healing and takes place concurrently during all phases of the reparative process. To restore anatomical continuity, epithelial cell migration starts from the wound edges, within few hours post wounding. the remodeling phase is responsible for the development of the new epithelium already formed during the proliferative phase, that is, the final scar tissue. Chronic wounds are those that fail to progress through the normal stages of healing and they do not repair in an orderly and timely manner. Many wounds that are perceived to be non-healing are in-fact simply just not provided with the right conditions in which to heal or could be due to frequent interferences by the patient, tension exceeds the myofibroblasts pull to approximate wound

edge, prolonged or excessive pressure can lead to ischemia, inadequate tissue oxygenation, or vasoconstriction due to sympathetic over activity. Furthermore, moisture retention in the wound is vital for cellular communication and migration, enhancing the repair phase. Inadequate surgical debridement of devitalized tissues is devastating for wound healing, excessive administration of steroids also negatively impacts on the healing process and closing a wound over non-viable/contaminated tissue. Nutritional deficiencies impair wound healing and interfere with the ability of the body to fight infection, hence, retard wound healing process.

8.0 Conclusion

Most wounds can be encouraged to heal if the contributory factors as stated in the summary are recognized and addressed. It is always critical to get an accurate history of the patient and the wounding episode. The most common reason by far for failure to heal is inappropriate management of the wound. Check through the management list first to ascertain if the wound has been dressed appropriately, attended to or the patient has been nursed in the proper manner. Educate the patient/ client on the importance of wound care and management, ensure you get them involved. At the same time, attain to any underlying host factors that may be playing a role in delaying wound healing. There is need for cost effectiveness, rational strategy for the use of advanced products in wound management.

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