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Physiology of Cutaneous Wound Healing: A Narrative Review Article

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Abstract

Purpose: Skin is the most important organ of the body and maintains its integrity is critical in good health. Severe skin damage is life-threatening and repairing restores its tissue integrity and delay in it endangers health. According to the importance of wound healing and the fact that not treated wounds may decrease quality of life, many studies have investigated the effect of some natural and chemical substance on the length and quality of wound healing to find out beneficial interventions that rapidly and economically treat it. This review aimed to describe the physiology of cutaneous wound healing and some negative and positive factor with a focus on exercise. **Methods:** An electronic search without any time limitation was performed on the PubMed, Google scholar and web of science databases to find published articles in English. The keywords were wound healing, exercise, and physiology. According to relation to subject, similarities, and differences 48 articles were selected and reviewed. **Results:** wound healing is a complicated physiology process that consists of four consecutive overlapping stages. Disruption in each stage disturbs wound healing. Many chemical and herbal compounds are used to speed up wound recovery due to their anti-inflammatory property. Exercise is one of the effective factors in wound healing and many studies evaluated effect of different protocol of exercise on it. The results of studies show that aerobic exercise due to its anti-inflammatory and antioxidative effect is a beneficial method in shortening the length of wound healing, especially in aged, fat, and diabetic individuals. **Conclusion:** Moderate intensity aerobic exercise as a complementary medicine is a good intervention in the treatment of impaired and chronic wounds.

***Keywords**:* Physiology, Exercise, Wound Healing

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INTRODUCTION

Skin is the largest organ of the body that covers the entire surface and prevents bacteria, viruses and other exogenous antigens enter the body and water move in and out (Christian, et al., 2006), it plays a pivot role in different processes such as protection from chemicals and pathogens, vitamin D synthesis initialization, excretion and thermal regulation (Tottoli, et al. 2020). According to the pivotal role of skin in maintaining good health its integrity is important, if wounded, its ability to heal quickly and effectively is essential to sustain good health (Christian, et al., 2006). A suitable wound healing is return to normal anatomical structure, function and appearance (Tottoli, et al. 2020). Severe skin damage can be life-threatening (Tottoli, et al. 2020). Impaired healing leads to chronic wound, ulcers formation, and excessive scarring (Adams, Sabesan, & Easley 2006). Impaired healed wound is a public health problem and many people deal with it (Keylock & Young, 2010). Wound healing has a significant economic impact on world healthcare. It costs the health system about 28.1 billion to 96.8 billion dollars per year (Sallehuddin, Nordin, Idrus & Fauzi, 2020). One of the major health problems is impaired cutaneous wound healing in pathologic situation like diabetes that leads to limb amputations (Pence & Woods, 2014). Due to the high prevalence of diabetes, malignant tumors, infections, and vasculopathy the rate of chronic wounds rises that has severe economic burden (Zhang, et al. 2020). In Pathologic situation Poor wound healing, impairs skin regeneration and decreases the quality of life and results in pain, and immobility (Wolfe, 2013). Given the importance of wound healing and the fact that not treating open wounds may lead to local infection and ultimately cancer. Many researches have been done on how to promote wound healing (Alah Gahi, Shiravi, & Hojati, 2016). There are many chemical and herbal medicines and compounds that can help to speed up recovery. These drugs and substances that are used in therapy are the results of research on animal and clinical models. Each intervention that accelerates wound healing has a critical role in preventing health problem due to the problem of delayed wound healing, So a beneficial intervention is essential to rapidly and economically treat it (Keylock & Young, 2010). It is important to consider effective, low-cost, and practical methods of wound healing (Javadi, et al. 2018). Many Studies

have been done to obtain a new and effective strategy of wound therapies to reduce the costs and provide long-standing relief and prevent scar forming (Tottoli, et al. 2020). According to the importance of wound healing in heaths, this study aims to review the physiology of wound healing and some effective factor with a special focus on exercise as complementary medicine.

METHOD

An electronic search without any time limitation was performed on the PubMed, Google scholar, and web of science databases that published in the English language. The keywords were wound healing, exercise. According to similarities or differences between the results and relation to subject 48 articles were selected and reviewed.

RESULTS

Wound healing physiology

The skin has regenerative property to restore tissue integrity (Saghazadeh, et al. 2018). Wound healing is a unique mechanism that involved many factors and cells (Zhou, Liu, Yang, Mi, & Ye, 2016). It is a dynamic process and consists of 4 precisely programmed overlapping phases included homeostasis, inflammation, proliferation, and remodeling, each stage must occur in appropriate order, time, and duration Any disturbance in each phase can delay wound healing or lead to non-healing chronic wound (Boucek, 1984). All 4 phases of Wound healing are interrelated and overlap (Gosain, & DiPietro, 2004). Acute wounds pass the normal wound healing phase, while chronic wounds display prolong inflammation phase (Tottoli, et al. 2020). These phases are inter-depended and Success in later phases is dependent on the Success in the preceding phase (Christian, et al., 2006). Every disruption in each phase leads to a delay in wound healing or non-healing chronic wound (Pence & Woods, 2014).

Homeostasis:

Homeostasis begins from the onset of injury till several hours after (Adams, Sabesan, & Easley 2006). It happens within 30 minutes post-trauma (Pence, 2012). In this phase as the first response to injury, Vessels constricts to control bleeding and clot forms. The Clot releases growth factors and pro-inflammatory cytokines (Boucek, 1984). Platelets and inflammatory cells rush to the injured area. Platelets

induce vasoconstriction that reduces blood flow to the wound bed (Saghazadeh, et al. 2018). The trapped Platelets in clot release vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), insulin growth factor (IGF), interleukin 1 (IL-1) (Saghazadeh, et al. 2018), and provide matrix for cell migration VEGF is critical for wound healing and is secreted by neutrophils, macrophages and platelets and stimulated angiogenesis (Roy, Khanna, & Sen, 2008).

Inflammatory phase:

After the cession of bleeding second stage, inflammatory phase begins, in this stage inflammatory cells (neutrophils, macrophages and lymphocytes) migration to wound initiates (Boucek, 1984). Monocyte differentiates to macrophages (Adams, Sabesan, & Easley 2006). In a normal wound, Inflammation lasts about 2-5 days and ends when the harmful agents are removed (Adams, Sabesan, & Easley 2006). Platelets release many cytokines and growth factors which lead to an inflammatory response that serves to remove bacteria and other pathogens in the wound (Keylock & Young, 2010).

Some study mentions Inflammation phase duration, is from the beginning of injury till the third day (Oki, & Amalia, 2020). In this phase, inflammatory cells migrate to the injured area and release pro-inflammatory cytokines and growth factors, digest foreign materials and increase vascular permeability (Gosain, & DiPietro, 2004). In the inflammatory phase, in the first 24 hours after injury, the number of neutrophils reaches to a maximum level and decrease after 3 days. Within 18-24 hours after wounding, the number of macrophages reaches the maximum, and on the fifth day, it is the majority of wound cells {Wolfe, 2013 #59}. The inflammatory phase can be divided into two stage early inflammation (24 - 48 h after wounding) with the influx of neutrophils and later inflammation (48 - 72 h after wounding) with the influx of monocytes and macrophages to the wound to remove germs {Roy, 2008 #79}.

A low level of inflammation is necessary for faster wound healing and its high level delays it (Keylock & Young, 2010). The inflammatory phase duration is about 5–7 days that removes contaminating debris and control microbial infection. In the inflammatory phase influx of neutrophil for infection control and

macrophage accumulation to initiate repair occur. Release of inflammatory chemokine (i.e., IL-1 and TNF-α) from the clot and injured cells in the margin of the wound is necessary for the migration of an adequate number of inflammatory cells to the wound bed (Christian, et al., 2006). Oxygen supply is critical for all process of wound healing like prevention of infection, angiogenesis, keratinocyte, migration and re-epithelialization, fibroblast proliferation and collagen synthesis, and wound contraction. As a result of vascular disruption and oxygen consumption of active cells, Wound tissue is hypoxic. Temporary low oxygen and the lactic acid act as a signal to stimulates wound healing and production of cytokine and growth factor and initiation cell proliferation, migration, chemotaxis, and angiogenesis in the wound bed, in prolonging hypoxia, wound healing is impaired (Boucek, 1984).

In the Inflammatory phase, foreign material and contaminating micro-organisms are removed from the wound. The prolonged inflammatory phase leads to chronic and not healing wound (Boucek, 1984). Hypoxia stimulates the secretion of cytokine and growth factor from macrophages, keratinocytes, and fibroblasts. Both hypoxia and hyperbaric oxygen produce reactive oxygen species (ROS), which act as a cellular messenger. For optimum wound healing, appropriate level of oxygen and ROS is crucial. Excessive ROS damage wound and tissue. Inflammation is necessary for the elimination of contamination, but its elongation enters the wound to a chronic state (Boucek, 1984).

Keratinocytes, macrophages, fibroblasts, platelets, and endothelial cells secrete VEGF that stimulate the formation of new blood vessels. Platelets and macrophages release PDGF and EGF that activate fibroblasts to produce collagen and proliferation (Zogaib, & Monte-Alto-Costa, 2011). Low-level endogenous H2O2 supports vascular growth and increases tissue vascularization (Roy, Khanna, & Sen, 2008). Respiratory burst in Neutrophils and macrophages release ROS, which kills bacteria and prevent infection and promote dermal wound repair. ROS induce the expression of vascular endothelial growth factor (VEGF) in keratinocytes and macrophages (Sen, et al. 2002). In the wound, destruction of the arteries restricts blood flow, and reduced oxygen delivery is one of the main factors that delays wound healing.

About 4 days after injury new capillaries form and the wound appearance is granular that names granulation tissue. Macrophages, fibroblasts, and blood vessels are the main component of granulation tissue (Bermudez, et al. 2011). In this phase activated Complement system and coagulation substance secrete vasoactive mediators and chemotactic factors that attract leukocytes to the injury. At this stage, mast cells release histamine and other active amines that produce signs of inflammation around the wound {Keylock, 2010 #77}. Neutrophils migrate to the injury within 24 h after injury and remove pathogens, foreign material, damaged matrix components and dead cells. On the second day after wounding, monocytes and lymphocytes migrate to the wound and differentiate into macrophages that phagocyte necrotic tissue, pathogens and form granulation tissue and produce growth factors (such as TGF-β, PDGF, tumour necrosis factor -α, TNF-α) and cytokines such as (IL-1, IL-6) (Saghazadeh, et al. 2018). Newly formed capillaries Supply oxygen and nutrients for growing tissue. Basal keratinocytes migrate from the wound margin and proliferate, differentiate and form a cover over the wound area. Fibroblasts migrate from bone marrow to activate and synthesize collagen, fibronectin, and hyaluronic. The fibroblast differentiates to myofibroblasts that close the wound surface (Saghazadeh, et al. 2018). The secreted cytokines and growth factors lead to an inflammatory response that removes bacteria and pathogens. Macrophages play an important role such as the killing of pathogens, phagocytosis, wound debridement, production of cytokines and growth factors, cell recruitment, and stimulating angiogenesis (Keylock & Young, 2010).

Proliferation phase

The third stage is proliferative phase begins at the end of the inflammatory phase (Alah Gahi, Shiravi, & Hojati, 2016). Proliferative phase consists of re-epithelialization, neo-vascularization, and granulation tissue formation {Christian, 2006 #80} It begins on day 4 and continues until day 21 (Adams, Sabesan, & Easley 2006). Some study reported this phase starts about 2–3 days after wounding and last till wound closure. In this phase, inflammatory cells and factors are reduced and fibroblast proliferation and collagen deposition, angiogenesis, tissue granulation, re-epithelialization, and wound closure

restructure the wound. Angiogenesis is an essential part of granulation tissue and initiation of re-epithelialization (Keylock & Young, 2010).

Release of pro-inflammatory cytokines, including IL-1, IL-6, IL-8, and tumor necrosis factor- α (TNF-α) from Neutrophils and macrophages play a critical role in the initiation of the healing cascade. These cytokines are necessary for wound repair. Healing time in IL-6 deficient mice is 3-fold more than healthy wild-type (Christian, et al., 2006). Several days after the beginning of the proliferative phase, capillary grows and granular tissue form. Fibroblasts synthesize collagen and re-epithelialization begins to close the wound (Gosain, & DiPietro, 2004). The clot and the surrounding tissue of the wound release pro-inflammatory cytokines and growth factors. In The proliferative phase epithelial cell proliferate and migrate to cause re-epithelialization (migration and proliferation of wound-edge keratinocytes). In this phase, fibroblasts produce extracellular components of the matrix like collagen, glycosaminoglycan and proteoglycan (Boucek, 1984). Insulin-like growth factor (IGF-1) by increasing neovascularization improve chronic wound healing via vascular endothelial growth factor (VEGF) dependent mechanism. After day 7 Keratinocyte migrations is necessary for wound closure. In chronic wounds epidermal cell migration is impaired and IGF-1 expression quickens it (LeSaint, et al. 2014). Nitric oxide, cytokines and growth factors stimulate Re-epithelialization. 2–3 days after injury Keratinocytes in the basal layer of the wound border and epithelial stem cells from hair follicles and sweat glands nearby dermis to the wound cover the wounded surface and secrete proteins to rebuild the basement membrane. Fibroblasts promote wound healing by producing cytokines, chemokines, and growth factors that enhance angiogenesis (Adams, Sabesan, & Easley 2006).

Remodeling phase

The end phase of wound healing is remodeling that lasts for a long time (Gosain, & DiPietro, 2004). It begins from the end of the granulation tissue formation (48). Remodeling phase duration is from 21 days till 1 year after wounding (Adams, Sabesan, & Easley 2006). Following the synthesis of the extracellular cellular matrix, the final stage of wound healing (remodeling phase) begins. it lasts a long time (Boucek, 1984).

When the re-epithelialization completes, the remodeling phase begins. Fibroblastic cells transform to myofibroblasts that contract the wound (Zogaib, & Monte-Alto-Costa, 2011). Contraction of the wound occurs throughout the remodeling phase by myofibroblasts (Pence, 2012). In the remodeling phase fibroblasts differentiate into myofibroblasts that contract the wound (Adams, Sabesan, & Easley 2006). Fibroblasts Synthesize collagen and glycosaminoglycans, which increases steadily until the third week to reach a point of equilibrium, the point that collagen synthesis and breakdown are equal (Alah Gahi, Shiravi, & Hojati, 2016). Fibroblasts synthesize extracellular matrix, which provides a framework for cell migration and proliferation, and increases wound tensile strength (Alah Gahi, Shiravi, & Hojati, 2016). In this phase collagen III exchange for collagen I (Adams, Sabesan, & Easley 2006).

Within 3-6 month, the newly formed scar degenerates and changes to soft and mature tissue. In this phase, deposition of the extracellular matrix (ECM) is more than its degradation (Zogaib, & Monte-Alto-Costa, 2011). At the end of the remodeling phase wound tissue is resemble normal tissue (Pence, 2012). Remodeling phase involved in restoring tissue structure and function (Christian, et al., 2006). The maximum tensile strength of healed wound is maximum of 80 % of normal skin (Adams, Sabesan, & Easley 2006). Excessive proliferation results in scarring or keloid formation (Sallehuddin, Nordin, Idrus & Fauzi, 2020). In this phase-type III, collagen replaces by type I collagen and readjusts to increase the tensile strength of the tissue to normal tissue. Fibroblasts and other cells secrete matrix metalloproteinase enzyme (MMPs) that degrade ECM and is a key factor in wound repair (Saghazadeh, et al. 2018). In remodeling phase change in composition and structure of the extracellular matrix, increase in tensile strength (Keylock & Young, 2010). Sometimes complete epithelialization of the wound area is not performed and leaves a scar. The scar is an accumulation of fibrotic cells that may limit the normal functions of the organ (Nurkesh, Jaguparov, Jimi & Saparov, 2020).

The effective factors on wound healing

The main effective factors in wound healing are oxygenation, age, sex hormones, stress, diabetes, obesity, medications, alcoholism, smoking, and nutrition (Boucek, 1984). Some factors that affect wound healing

are local that directly effect on wound and others are systemic that indirectly influence (Alah Gahi, Shiravi, & Hojati, 2016). Some medication (such as steroids), lifestyle (such as sedentary), disease (such as diabetes) and biological situation (such as ageing) delay wound healing (Keylock & Young, 2010). Many factors like topical hormones, norepinephrine, hyperbaric oxygen, exercise and growth factors and nutrition can improve wound repair (Keylock & Young, 2010; Keylock, et al. 2008).

Systemic factors such as age, the presence of vascular or metabolic diseases, some drug may affect wound healing (Tottoli, et al. 2020).

For instance, because of the positive effect of estrogen on Wound healing processes, female mice heal faster than their male counterparts (Pence, 2012). Studies show growth factors promote tissue regeneration but due to their dangerous side effects such as tumors their usages not be recommended (Nurkesh, Jaguparov, Jimi & Saparov, 2020).

Common wound care categorizes into modern and traditional treatment. Traditional-based medicine uses plant compounds such as Nigella sativa and honey to speed up wound healing (Sallehuddin, Nordin, Idrus & Fauzi, 2020) and modern- based such as use laser and hydrogel (Sallehuddin, Nordin, Idrus & Fauzi, 2020). The herbal healing effect is mediated by the anti-inflammatory and antioxidant property, but they can't permanently replace the use of current effective drugs and modern dressing (Sallehuddin, Nordin, Idrus & Fauzi, 2020). Hydrogels are composed of hydrophilic substances that maintain the wound moist and help in wound healing (Shi et al. 2020).

Negative factors on wound healing

1. Anti-inflammatory medications such as glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), and chemotherapeutics interfere with platelet function or inflammatory processes and slow down the speed of wound repair.
2. Glucocorticoid through reductive expression of inflammatory mediators and chemokines inhibit the influx of inflammatory cells to the wound environment and ultimately impair wound healing (Pence, 2012). Glucocorticoids as an anti-inflammatory agent suppress immune cells and modulate Th1-mediated immune responses and delay the healing process as a result of increasing the duration of the inflammatory phase. Stress decreases collagen fibre

synthesis (Monte-Alto-Costa, Saguie, & Romana-Souza, 2015). Topical application of glucocorticoids produces inflammatory cytokines such as IL-1, IL-6, IL-8 and TNF-α and inhibits keratinocyte growth factor (KGF) expression (Ebrecht, et al. 2004).

3. One of the risk factors that impair wound healing is sleep deprivation because inadequate sleeping causes dysregulation of circulatory cytokines.
4. Malnutrition is an inadequate intake of glucose, polyunsaturated fatty acids, protein, vitamins and consumption of heavy alcohol that delay wound healing. It is well known that smokers heal wounds more slowly than nonsmokers (Christian, et al., 2006).
5. Obesity, diabetes, stress and ageing are accompanied by low-level inflammation which impairs cutaneous wound healing (Pence & Woods, 2014). In elderly and obese individuals, basal levels of inflammation increase (Pence, 2012). Prolonged inflammation is associated with high levels of pro-inflammatory chemokines and cytokines in wound bed in obese and aged individuals that induce prolongation of the inflammatory phase and impede wound healing (Pence, DiPietro & Woods, 2012). Adipocytes and macrophages in the adipose tissue produce adiponectin, which has a bad effect on immune and inflammatory systems (Alah Gahi, Shiravi, & Hojati, 2016). In elderly individuals decrease in interleukin-15 (IL-15) increases markers of growth stop indicators, and decreases keratinocyte and fibroblast growth factor (Wong, Crane, Kuo, Kim, & Crane, 2019).
6. Chronic stress by increasing circulatory glucocorticoid hormone slows wound repair because glucocorticoids reduce migration of inflammatory cells, reduce pro-inflammatory cytokines IL-1β, IL-6, and TNF-α in the wound area, damage anti-bacterial function, and finally slow healing. Delayed wound repair in depressed and nervous people is 4 times more than in healthy people. In surgery wound stress delay healing (Christian, et al., 2006). Psychological stress delay wound healing via deregulation of the immune system (Alah Gahi, Shiravi, & Hojati, 2016).
7. Prolonged hypoxia as a result of insufficient perfusion and low angiogenesis is harmful to wound healing. Hypoxia potentiates

inflammation and increases ROS (Alah Gahi, Shiravi, & Hojati, 2016).

8. A low concentration of ROS disinfects the wound and regulates many signal transduction and gene expression that facilitates healing (Roy, Khanna, Nallu, Hunt, & Sen, 2006). Diabetic foot is a problem in diabetes. In diabetic wound decreased angiogenesis and decreased production of growth factor, abnormal inflammatory and immune response, prolonged inflammatory phase, decreased contraction of the wound, and imbalance between Construction and decomposition of extracellular components and their remodeling have been demonstrated (Eraydin, & Avşar, 2018). Obesity, diabetes, stress and ageing induce a chronic low-level inflammation that hurts the healing process (Pence & Woods, 2014).

Positive factors on wound healing

Many researches have been done on wound healing and as a result, various materials have been prepared and introduced to accelerate wound healing. Natural substance like Nigella sativa, honey, and green tea extract has been shown shorten wound healing time due to stimulation of angiogenesis, improvement fibroblast proliferation, and collagen synthesis and reduction of inflammation (Sallehuddin, Nordin, Idrus & Fauzi, 2020). The beneficial effect of honey in wound healing is the result of its Low pH, hydrogen peroxide content, absorption of excessive wound exudate, antibacterial and anti-inflammatory properties (Javadi, et al. 2018). Fibroblasts require an acidic environment for activation and Low pH of honey provides optimal conditions. Lysozyme of honey has a potent antimicrobial property and stimulates or inhibits the release of several cytokines (tumor necrosis factor-α, interleukin-1β and interleukin-6) from monocytes and macrophages (Martinotti, & Ranzato, 2018). Thus healing properties of honey are due to its antimicrobial and anti-inflammatory property, moisturizing the wound bed, osmotic effects, diminishing oedema, quickening angiogenesis and granulation tissue formation, accelerating epithelialization, increasing activities of lymphocytes and phagocytes, and debridement of necrotic tissue (Pence, 2012). Topical application of honey increases granulation tissues depth, accelerates angiogenesis, elevate fibroblast density, and subsidence inflammation in wound bed (Riahi, et al. 2008). According to study Olive oil speed up wound

healing because it contains essential fatty acids (linoleic acid and linoleic acid) and antioxidant, antimicrobial, and anti-inflammatory property (Karimi, et al. 2019). Grapeseed oil interferes with cell proliferation and angiogenesis due to its antioxidant and anti-inflammatory properties (Alah Gahi, Shiravi, & Hojati, 2016). Topical application of sodium phenytoin ointment 1% increase fibroblasts, granulation tissue formation and Collagen production in the bed of wound (Riahi, et al. 2006). The most common, inexpensive and safe recommendation in the prevention and treatment of chronic wounds is exercise (Keylock & Young, 2010). In the next section, we review the Studies that have done about the effect of different protocols of exercise on wound healing.

Effect of exercise on the speed of wound healing

Exercise as complementary medicine can be used as an intervention strategy in clinic to accelerate wound healing (Pence & Woods, 2014). Even one session of exercise increases the number of circulatory endothelial progenitor and angiogenic cells that improve vascular synthesis. Overproduction of ROS during the exercise augmented inflammation which stimulates angiogenesis. Exercise increases Nitric oxide production that is upstream of VEGF (Roy, Khanna, Nallu, Hunt, & Sen, 2006). A study showed that exercise has an important role in the healing of any type of wounds for example exercise promotes oral mucosal wound healing and in other studies, it is demonstrated Kegel exercise in the first week of post-partum, significantly accelerate perineum wound healing in comparison with sedentary ones (Gustirini, Pratama, & Maya, 2020). Exercise training is a beneficial way of improving healing in venous leg ulcers (Tew et al. 2015). Exercise improves wound healing in diabetic mice and healthy elderly humans (Bolton, 2019). In diabetics and elderly individual production of ROS increases and result in delayed wound healing (Keylock & Young, 2010). Ankle exercises in diabetes have a positive effect on lower limb wound healing by rising blood flow (Flahr, 2010). In Lively Legs program walking and leg exercise accelerate wound closure (Heinen, et al. 2012). During walking, calf muscles act as pomp and improve blood circulation. In patients with venous leg ulcers, 12-week exercise intervention as an adjunctive treatment to standard care

significantly speed up ulcer healing (O'Brien, Finlayson, Kerr, & Edwards, 2017).

Also, exercise has a positive effect on the homeostasis phase through the increasing activity of platelets and coagulation factors (Pence, 2012). Researchers showed that exercise increases the speed of cutaneous wound healing in aged and obese mice (Zhou, Liu, Yang, Mi, & Ye, 2016). Exercise promotes wound healing by reducing systemic and local inflammation in obsessing and aged individuals and significantly reduces the duration of the inflammatory phase in aged mice (Pence & Woods, 2014). Regular moderate exercise prevents oxidative and nitrosative stress by potentiating antioxidant defiance/repair systems (Riahi, Mohammadi, & Sobhani, 2014). Many epidemiological studies demonstrated regular exercise decreases inflammatory markers {Keylock, 2010 #77} as a result of regular exercise anti-inflammatory property (Alah Gahi, Shiravi, & Hojati, 2016) inflammatory cytokine level is lower in exercised aged mice in comparison with sedentary ones (Keylock & Young, 2010). the greatest effect of exercise is 1-5 days post-wounding, especially on the first day. This shows that exercise affects the early stages of wound healing (inflammatory phase) (Pence, 2012).

It seems that the effect of exercise on inflammation depends on the length and intensity of exercise (Keylock & Young, 2010). Because exercise duration and intensity are an important factor in the regulation of pro-inflammatory molecules concentration (Zogaib, & Monte-Alto-Costa, 2011). Regular exercise reduces CRP level and suppresses systemic low-grade inflammation. The contracting muscle produces IL-6 which is 100-fold more than resting situation (Mathur, & Pedersen, 2008).

In exercising mice inflammatory cytokines level is low in the wound area (Keylock & Young, 2010). Exercise increases systemic levels of anti-inflammatory cytokines. Contracting skeletal muscle is an endocrine organ and releases myokines that may mediate the beneficial effects of exercise on wound healing IL-6 is the first cytokine that raises up to 100-fold in circulation during exercise. The rate of increase is proportional to exercise duration, intensity, and muscle mass involved in the training exercise. IL-6- is an anti-inflammatory and immunosuppressive cytokine that is produced by contracting muscle

fibers during exercise and followed by increased circulatory levels of other anti-inflammatory cytokines such as IL-1ra and IL-10. IL-6 inhibits the production of TNF-α and IL-1 (Mathur, & Pedersen, 2008).

Interleukin-15 is an essential mitochondrial signal that helps in wound closure. Its effect is mediated by the reduction of the growth arrest factor and increase in keratinocyte and fibroblast growth. The positive effect of exercise on wound healing of elderly patients is mediated by circulating IL-15 (Wong, Crane, Kuo, Kim, & Crane, 2019). In aged mice exercise increases circulatory IL-15, which activate signal transducer and activator of transcription 3 (STAT3) signaling pathway, reduces growth arrest, and increases keratinocyte and fibroblast (Wong, Crane, Kuo, Kim, & Crane, 2019).

Regular exercise may decrease levels of inflammatory markers. There is a reverse relationship between activity and inflammation. C-reactive protein (CRP) level inactive individuals are less than their sedentary counterpart (Keylock & Young, 2010). A higher level of exercise is associated with fewer inflammatory markers and diseases. 12 weeks of moderate exercise reduce pro-inflammatory cytokines. The inflammatory effect of exercise depends on the age of subjects, the length and intensity of exercise, method and time of measured inflammatory indicator, and previous subject's fitness level (Keylock & Young, 2010).

Exercise has a positive effect on the immune system and endocrine function and psychological problem such as stress. Short-term exercise has no positive effect on wound healing (Christian, et al., 2006). The literature that evaluates the effect of exercise training on wound healing has used different training protocols. Some used high intensity (about 90% VO2max), and the others use moderate intensity (about 70% VO2max) that mimic the volume of recommended exercise for the general population to promote health. In study of the effect of exercise intensity on the acceleration of skin wound healing it was found that moderate-intensity training (70% VO2max) leads to better wound closure compared to high intensity (80% VO2max) and strenuous intensity (90% VO2max) (Zogaib, & Monte-Alto-Costa, 2011). Heinen et al reported the best intensity in wound healing in diabetes is approximately 60% VO2 max (Wolfe, 2013). The strong evidence indicated that chronic moderate-intensity exercise (64–76% of maximal

heart rate) activates several signaling pathways and produces anti-inflammatory and antioxidant response (Amatriain-Fernández, et al. 2020). Strenuous exercise caused inflammatory reaction due to the overproduction of free radicals (Zogaib, & Monte-Alto-Costa, 2011) and increases TNF-α and IL-6 levels in serum that attracts inflammatory cells in the wound bed and delay healing (Saguie, Romana-Souza, Martins, & Monte-Alto-Costa, 2017).

Pence et al. reported short-term treadmill exercise (3day before and 5day after wounding) had no positive effect on the speed of wound healing in lean rat but accelerate it in obese ones. This effect was depended on alterations of pro-inflammatory cytokines interleukin-1 and tumor necrosis factor (Pence, DiPietro & Woods, 2012).

Emery et al. showed that three months of aerobic exercise in a moderate-intensity fastened wound healing process in older adults. They attributed this positive effect to the enhancement of neuroendocrine response due to the training exercise. Exercise reduces resting cortisol levels and increases the response of cortisol to stress and enhanced neuroendocrine responsiveness. Keylock et al showed that 30 min per day at 70% VO2max 3 days before and 5 days after wounding speed up cutaneous wound healing in old mice. Exercise reduces TNF- α and pro-inflammatory chemokines in tissue wounds of aged mice during 1-5 days after wound healing. The possible mechanisms may be an increase in oxygen partial pressure, blood supply, neuroendocrine response to exercise and mechanical load (Keylock, et al. 2008). Polymorphonuclear (PMN) and macrophages in the wound area need Oxygen (O2) in order to phagocyte microorganisms and necrotic tissue (Flahr, 2010). Moderate intensity exercise by improvement in tissue oxygenation accelerates the wound healing process (Keylock & Young, 2010). 12 weeks of moderate swimming exercise after tooth extraction increased the number of PMN and macrophages in the wound site in rats (Keylock & Young, 2010). The number of PMN and macrophage as an indicator of wound healing in training aerobic exercises were more than anaerobic exercises and in both of them were more than sedentary ones. Both aerobic and anaerobic exercises speed up wound healing, although aerobic exercise is better than anaerobic exercises (Oki, & Amalia, 2020). Anaerobic exercises increase ROS production in wound bed that disturbs healing

(Oki, & Amalia, 2020). Much evidence supports the positive role of moderate aerobic exercise in the reduction of oxidative stress by increasing antioxidant enzyme activities (Keylock & Young, 2010). Oxidative stress delay wounds healing. Evidence indicated exercise by increasing antioxidant enzyme activities prevents damage of ROS. Hoffman-Goetz et al. reported 16 weeks of exercise increased the expression of catalase and glutathione peroxidase in mice. One-year training increased glutathione peroxidase and superoxide dismutase in rats and six months of aerobic exercise increased resting levels of glutathione peroxidase and superoxide dismutase. It seems regular exercise by increasing the body's systemic antioxidative defence prevent oxidative stress and accelerate healing (Keylock & Young, 2010). Conditions such as physical exercise result in increased production of ROS such as H2O2 that supports vascular growth and increases tissue vascularization (Roy, Khanna, & Sen, 2008).

Exercise improves impairment in physiological function in the older person. Emery et al. reported Wound healing was faster in the old individual who did exercise. It may be due to the role of exercise in neuroendocrine regulation, reduction in resting cortisol levels and increase in blood flow and oxygen tension in the cutaneous wound (Emery, Kiecolt-Glaser, Glaser, Malarkey, & Frid, 2005).

Stress increases inflammatory cells and decreases angiogenesis and differentiation of the fibroblast to myofibroblast and low matrix deposition in the wound. Moderate exercise training before wounding reduces this effect due to the anti-inflammatory mechanism.

Delay in wound healing is exacerbated When stress and exercise were applied simultaneously (Saguie, Romana-Souza, Martins, & Monte-Alto-Costa, 2017).

One problem in the refractory wound is inadequate blood supply in the border of the wound. Regular low-intensity endurance exercise improves wound healing by improving vascular regeneration and local blood supply in the wound area through elevating endothelial progenitor cells (EPCs) and circulatory vasoactive factors in peripheral blood (Zhou, Liu, Yang, Mi, & Ye, 2016).

Oxygen is important in the synthesis of connective tissue and the prevention of wound infection. Exercise provides adequate oxygen supply to wound tissue and help in healing. The clinical study indicated

that high-level physical activity after surgery enhances surgical wound healing (Whitney, & Parkman, 2004). Regular low-intensity endurance exercise improves wound healing, elevate endothelial progenitor cells (EPCs) and circulatory vasoactive factors in peripheral blood, which improve vascular regeneration and local blood supply in the wound area. An increase in the number of circulating EPCs in the peripheral blood and an increase in the secretion of vasoactive factors are two main Indicators in the capacity of low-intensity exercise in promoting wound healing. The number of circulating EPCs and vasoactive factors such as VEGF, eNOS and bFGF were higher in the exercise group than the non-ex group (Zhou, Liu, Yang, Mi, & Ye, 2016). One-month low-intensity exercise promotes wound healing by increasing the vascular density around the wound as a result of an increase in vessel regeneration that restores blood supply. Exercised rats had a higher wound healing, it seems low-intensity treadmill exercise accelerates wound healing (Zhou, Liu, Yang, Mi, & Ye, 2016).

Moderate exercise 3 days after tooth extraction significantly increased expression of VEGF. Reduction of inflammation as a result of exercise is obtained with a decrease in visceral fat mass, decrease in the Toll-like receptors and increase in anti-inflammatory cytokines. Exercise reduces the infiltration of macrophages and monocytes into the tissues. Regular exercise increases adrenaline, which induces the expression of VEGF in macrophages. Hypoxia stimulates neovascularizing and increased Hypoxia-inducible factor-1 (HIF-1) in the wound area. HIF increases the expression of several genes that are involved in angiogenesis (Irmawati, Giffari, & Oki, 2018). VEGF and NO is necessary for angiogenesis. 4 weeks of endurance training increase capillary network. Exercise training increased the number of circulating endothelial progenitor and angiogenic cells and improved vascular function and NO synthesis (Roy, Khanna, & Sen, 2008). Exercise training increases collagen turnover in the skin. Zogaib et al. reported moderate-intensity exercise speed up healing in the trained individual. Exercise increases the turnover of collagen type I in connective tissue (Zogaib, & Monte-Alto-Costa, 2011).

Exercise increases the number of myofibroblasts in mouse patellar tendons (Szczodry, et al. 2009). Characteristic of exercise like length, frequency and duration of intensity are summarized in Table1. Studies

indicated exercise as a low- cost intervention is a beneficial strategy in the treatment of impaired wound healing (Pence & Woods, 2014).

Table1: Summarize of study that survey effect of exercise on wound healing. A review of studies shows that different exercise protocols have been used

Author/year/reference	Group	Experimental protocol	Results
Wu ZHOU (Zhou, Liu, Yang, Mi, & Ye, 2016).	two groups: exercise group and non-exercise group (N=20)	Both groups received dorsal wound operation. The rats in the exercise group were given treadmill exercise for one month, and the non-exercise group raised on the same conditions without treadmill exercise	wound area in the exercise group was smaller at the same time than the non-exercise group. the exercise group had a number of circulating EPCs and vasoactive factors than the non-exercise group. low-intensity exercise accelerates wound healing
Pence BD (Pence, DiPietro & Woods, 2012).	obese female mice	female mice fed a high-fat diet for 16 wk. Mice ran on a treadmill for 3 d before excisional wounding. On day 4, mice were wounded. Mice exercised for 5 d after wounding, and healing was assessed	obesity impaired wound healing, with significantly larger wound sizes ($P < 0.05$). Exercise did not improve healing in lean mice. wound size was significantly smaller in exercised obese mice compared with their lean counterparts ($P < 0.05$). There was no difference in gene or protein expression of proinflammatory cytokines. effect of exercise is independent of alterations in inflammation

K. Todd Keylock (Keylock, et al. 2008).	young (3 mo) and old (18 mo) female mice. Mice were divided to exercise and non-exercise groups.	The exercise group mice run on the treadmill at a moderate intensity of 30 min/day for 8 days. All mice were given four full-thickness dermal wounds, and the rate of wound closure was assessed daily for 10 days.	exercise reduced wound size in young mice ($P = 0.10$) exercise significantly decreased wound size in old mice ($P < 0.05$). TNF-α, KC, and MCP-1 were significantly lower in wounds of old mice than their control ($P < 0.05$) exercise accelerates the wound healing process in old mice as a result of the exercise-induced anti-inflammatory response in the wound
Garry A Tew (Tew et al. 2015).	Eighty adults with venous leg ulcer randomly assigned to receive usual care and the other group receive usual care plus a 12-week supervised exercise program.	exercise group did12-week supervised exercise program, 60-minute sessions of supervised exercise three time a week, each session involved a combination of treadmill walking, upright cycling and strength and flexibility exercises for the lower limbs. Participants were assessed before randomization and 3, 6 and 12 months after initiation of the experiment.	At 12-months median ulcer healing time was lower in the exercise group (13 vs 34.7 weeks)
Emery (Emery, Kiecolt-Glaser, Glaser, Malarkey, & Frid, 2005).	Twenty-eight healthy old adults (mean age 61.0 +/- 5.5 years) were divided to an exercise group (n = 13) or control group (n = 15).	exercise participants had acclimated to the exercise routine, all participants underwent an experimental wound procedure. Wounds were measured 3 times per week until healed to calculate the rate of late wound healing	A relatively short-term exercise intervention is associated with enhanced rates of wound healing among healthy older adults

Zogaib (Zogaib, & Monte-Alto-Costa, 2011).	Ninety males' mice were divided into three physical training groups: moderate (70% VO2max), high (80% VO2max), and strenuous intensity (90% VO2max) (N = 10)	Animals trained on the treadmill, five times/week, for 45 min for 8 weeks (E lesion: physical training until the day of the excisional lesion) or 10 weeks (E euthan: physical training for 2 additional weeks after excisional lesion). mice were submitted to a dorsal full-thickness excisional wound and sacrificed 14 days after wounding.	Moderate-intensity training (M) until lesion (M/E lesion) led to better wound closure than controls and M/E euthan ($P < 0.05$), and both moderate-intensity groups showed better re-epithelialization rates than controls (M/E lesion = 85.9%, M/E euthan = 96.4% and M/CG = 79.9%; $P < 0.05$). M/E lesion and M/E euthan groups showed the most mature granulation tissues among all trained groups and controls. moderate-intensity physical training improves skin wound healing.
Wolfe A (Wolfe, 2013)	female diabetic mice were randomly assigned to a sedentary control group, low-intensity treadmill exercise, high-intensity treadmill exercise	Mice were exercised for 30 minutes, five days a week, for three weeks on a 5% incline at 12 m/min (low intensity) or 18 m/min (high-intensity). Three days after exercise mice were wounded on the upper back.	low-intensity exercise t improved healing of wounds in T2D, not high-intensity exercise
Irmawati (Irmawati, Giffari, & Oki, 2018).	Rats were divided into control and exercise group	The exercise was a moderate exercise with 50% maximal work capacity, every day, for 2 weeks. The VEGF expression was assayed in macrophages 3 days after tooth extraction	exercise group had a higher expression of mean VEGF as compared to the control group. Moderate exercise increased the expression of VEGF during wound

O'Brien (O'Brien, Finlayson, Kerr, & Edwards, 2017).	63 Patients were randomized to receive either a 12-week exercise in addition to routine care intervention or usual care	12-week exercise intervention in conjunction with usual care	70% of intervention group and 53% control group Healed. participants who adhere to the exercise program are more likely to heal and have better functional outcomes than those who do not adhere to the exercises in conjunction with usual care (P = 0•045).
Andrea Monte-Alto-Costa (Monte-Alto-Costa, Saguie, & Romana-Souza, 2015).	mice divided in three groups: sham, stressed-sedentary and stressed-exercised	The exercised animals were submitted to a moderate intensity treadmill protocol for eight weeks. After 6 weeks of training, the stressed group was submitted to stress, until the end of the experiment. On the 8th week, two excisional wounds were performed. After the lesion, the exercise stopped	The Stressed-sedentary group presented higher amounts of inflammatory cells, and a thinner neo-epidermis, compared to the exercised group. Myofibroblasts and blood vessels with pericytes were increased in the exercised group. The Stressed-sedentary group presented less and immature collagen fibres than the exercised group. exercise impairs wound closure in stressed animals, but the formed scar seems to present a better quality

CONCLUSIONS

According to results of studies wound healing consist of 4 phase and disturbance in each stage lead to delay in wound healing. In Some situation like ageing, obesity, stress, and diabetes a chronic low-level inflammatory as a result of the increase in oxidative stress increases inflammatory phase duration that impairs skin regeneration. The most natural and synthetic substance like honey or green tea with reduction inflammation help in shortening wound healing length**.** it is well known that regular moderate-intensity exercise has an anti-inflammatory effect

through potentiating antioxidative system, increasing systemic levels of anti-inflammatory cytokines (e.g. IL-6), inhibiting the production of inflammatory cytokines, and reducing resting cortisol levels. In addition to the anti-inflammatory effect, regular exercise improves angiogenesis and increase local blood flow provides oxygen and nutrients to wound tissue, which is important in the synthesis of connective tissue and prevention of wound infection. Exercise potentiates the turnover of collagen in connective tissue and strengthens scar. Regular exercise speed up healing and short-term exercise has no positive effect on it. Strenuous exercise caused an inflammatory reaction that increases inflammatory cells and delays healing. Moderate intensity exercise as a low- cost intervention is a beneficial strategy in the treatment of impaired and chronic wound and shortening healing duration and can be recommended as complementary medicine in the clinic to accelerate wound healing.

Conflict of Interest

Authors declare no conflict of interest.

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