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The Importance of Iron in the Regeneration of Skin and Cutaneous Wounds

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ABSTRACT:

In this review paper, we explore the present state of information regarding the role that iron plays in the healing process of cutaneous wounds. Iron is an essential component in both the oxidative stress response as well as the photo-induced skin damage pathway. The ultraviolet (UVA) 320-400 nm region of the ultraviolet spectrum and physiologically accessible iron are the two primary contributors to oxidative stress in the skin. Reactive oxygen species (ROS) are also one of the primary causes of oxidative stress in the skin. In addition to this, we talk about the connections between iron deficiency, anaemia, and the healing of cutaneous wounds. There are two major categories to be found within this body of research. Early studies employed a range of experimental methods to determine anaemia or iron deficiency and concentrated on wound-strength rather than the influence of anaemia on macroscopic healing or re-epithelialization. These research were conducted to study the effect of anaemia on wound healing. In more recent investigations conducted on animals, innovative treatments have been examined with the goal of alleviating the effects of systemic iron deficiency as well as localised iron overload. Iron excess is associated with local cutaneous iron deposition, which is associated with multiple detrimental effects in both hereditary haemochromatosis and chronic venous illness. Anemia of chronic disease and dysregulation of local cutaneous iron haemostasis are associated with conditions such as rheumatoid arthritis (RA) and lupus erythematosus. Iron plays a key role in chronic ulceration, and conditions such as these are also associated with dysregulation of local cutaneous iron haemostasis. Iron is a potential therapeutic target in the skin by application of topical iron chelators and novel pharmacological agents, as well as in delayed cutaneous wound healing by treatment of iron

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deficiency or underlying systemic inflammation. This can be accomplished by applying iron chelators topically and utilising novel pharmacological agents.

Keywords: genetics, clinical symptoms, transferrin receptor, pro-inflammatory cytokines.

INTRODUCTION:

Iron is a necessary co-factor for proteins and enzymes that are involved in the processes of metabolising energy, respiration, synthesis of DNA, arrest of the cell cycle, and apoptosis. In the past ten years, significant progress has been made in the field of understanding the genetics of iron metabolism. As a result of these advancements, a number of new proteins have been discovered, one of which is hepcidin, an acute phase protein that serves as the master regulator of iron absorption and utilisation and is frequently activated in chronic diseases (1, 2).

Iron has been known for a very long time to be necessary for healthy skin, mucous membranes, hair, and nails. This has been the case throughout history. Angular chelitis, a swollen tongue, frail nails, kolionychia, and dry, brittle hair are some of the clinical symptoms of iron deficiency. Pale skin, pruritus, and a tendency to skin infection (impetigo, boils, and candidiasis) are all associated with iron deficiency.

Normal Physiology of Iron and Its Role in the Skin Role of Iron in the Skin

It is difficult to have a good grasp on the normal physiology of iron in the skin because of its complexity. It is well knowledge that the amounts of iron found in normal epidermis are assumed to span a wide range of values (3, 4). Iron levels also fluctuate within the normal dermis, and it is believed that they rise as a natural consequence of the ageing process (5).

In addition, proteins that contain iron have specialised functions, such as the metabolism of collagen by procollagen-proline dioxygenase (6, 7), which they do (Figure 1). Desquamation is the process by which iron is lost through the skin. Although the body does not actively excrete iron, the skin is an important organ in iron homeostasis because iron is lost via the skin (Figure 2). The active dissolution of desmosomes involved in keratinocyte cell-cell adhesion, which is thought to be caused by hydrolytic protease digestion, is one of the most prominent contemporary hypotheses concerning the fundamental mechanisms underpinning desquamation (8). It is believed that the desquamation of keratinocytes is responsible for 20–25% of the iron that is absorbed but afterwards lost (9). However, on a global scale, the daily loss of iron due to desquamation accounts for approximately 25% of the daily iron excretion from the urine (3). Evidence is emerging from genetic model mouse studies by Milstone et al (10) that both loss of iron by desquamation and local changes in epidermal iron metabolism have some role in systemic iron metabolism (these studies investigated three groups of mice: firstly mice overexpressing of HPV16 E7 gene, which causes a 3-fold increase in epidermal turnover; secondly mice overexpressing the transferrin receptor, which causes a 3–4 fold increase of epidermal iron in a skin sample; and finally mice In addition, gender-related

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disparities in iron status might be to blame for the fact that women live longer than men do. Men tend to have higher iron stores in their bodies. It is possible that the relative variation in iron levels seen in cells between the sexes is significant, not only from a physiological standpoint, but also in the context of pathological situations (11).

Iron, oxidative stress, and the damage caused by sunlight

The reactive oxygen species (ROS) that are produced in the skin as a result of exposure to the ultraviolet (UVA) 320-400 nm region of the ultraviolet spectrum are the primary contributors to oxidative stress in the skin. Because it is a transition metal that may exist in two stable states, namely Fe2+ (an electron donor) and Fe3+, iron plays an important part in the processes that are associated with oxidative stress (electron acceptor). Labile iron found inside cells can undergo redox cycling between its two most stable oxidation states, Fe2+ and Fe3+, and react with reactive oxygen species (ROS) like superoxide anion and hydrogen peroxide to produce hydroxyl radicals via the Fenton reaction or superoxide-driven Fenton chemistry (12).

UVA can cause reactive oxygen species (ROS) to be produced in skin fibroblasts, which can then increase oxidative damage in lysosomal, mitochondrial, nuclear, and plasma membranes. Necrotic cell death is the end outcome of the breakdown of the plasma membrane's integrity, which occurs in tandem with the depletion of mitochondrial ATP (13). Keratinocytes are regarded to be more resistant to membrane damage and cytotoxicity caused by UVA than skin fibroblasts are. This belief is based on the fact that keratinocytes are compared to fibroblasts. In vitro studies have shown that even though UVA causes lysosomal damage, ferritin degradation, and cytosolic labile iron release in keratinocytes, the absolute level of UVA induced labile iron release in keratinocytes is several fold lower than in fibroblasts. This suggests that there is a link between UVA induced labile iron release and keratinocyte resistance to UVA-mediated damage (14).

Anemia, a lack of iron, and the healing of cuts and wounds on the skin

The process of wound healing is one that is constantly changing and is highly regulated. It consists of cellular, humoral, and molecular systems (15).

Studies in the Laboratory Concerning Iron, Anaemia, and the Healing of Wounds

In the current body of research, there are two major camps that animal studies belong to. Early research on the impact that anaemia has on the healing process used a wide range of experimental approaches to determine whether or not the participants had anaemia or iron deficiency. Instead of focusing on initial macroscopic healing or histological investigations of re-epithelialization, they concentrated on wound strength research. In more recent research, novel treatments have been investigated with the goal of correcting the effect of systemic iron deficiency. These treatments include the topical application of iron-chelators to reduce iron at

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the specific site of inflammation, as well as their effect on pro-inflammatory macrophages in particular.

In-vivo Studies Investigating the Impact of Iron Deficiency on the Healing Process of Wounds

In the earliest experimental experiments on rodents, a diet of powdered milk was employed to determine whether or not there was an iron shortage.

It was discovered by Jacobson and colleagues (16) that anaemic mice that were given a diet consisting of iron-free powdered milk had a considerably lower wound breaking-strength than control mice that were fed chow. Young rats that were given a diet deficient in iron (powdered milk) and were treated to repeated bleeding to generate chronic anaemia had a lower wound tensile strength, according to the findings of Bains and colleagues (17). However, more recent research carried out by Macon and colleagues (18) came to the opposite conclusion; they found that IDA had no impact on the wound breaking strength. This may be a result of methodological flaws caused by the use of powdered milk to determine iron deficiency, as Waterman et al (19) demonstrated that control and anaemic rats fed powdered milk had slower wound contraction and reduced wound breaking strength in comparison with animals fed normal chow. This may indicate that the use of powdered milk to determine iron deficiency introduces methodological flaws.

Sandberg et al(20) .'s investigation on the impact of anaemia and blood volume on the strength of wound healing discovered that replenishing blood volume with dextran restored normal wound healing in a rabbit model that had undergone acute haemorrhage. This was the conclusion of their study. In rabbits that were made anaemic by bleeding and re-transfusing plasma, Heughan and colleagues (21) discovered that there was no substantial change in the oxygen tension (PO2) of the wound fluid. In addition, the weight of connective tissue was found to be larger at lower packed cell volumes. This was an initial observation that suggested that hypoxia had a negative influence on the synthesis of collagen.

Histological examination of excisional wounds in Wistar rats at 7, 14, and 21 days post-healing was the method that Oliverira-Sampaio and colleagues (22) used to assess the effect of delivering an iron-free diet for 15 days.

In animals with anaemia, exposure to LED light induced a considerable positive bio-modulation of fibroblastic proliferation, but exposure to laser light was more successful in enhancing proliferation in animals without anaemia.

The effect of iron shortage on the early stages of wound healing (re-epithelialization) or later resolution was not described in this study.

There are a number of different ways in which an iron deficit might slow the healing process of wounds. The available information points in the direction of hypoxia playing a significant

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influence. (Through its role in cell migration, cell survival under hypoxic conditions, cell division, growth factor release, and matrix synthesis) Hypoxia-inducible factor-1 (HIF-1) contributes to all stages of wound healing, and positive regulators of HIF-1, such as prolyl-4-hydroxylase inhibitors, have been shown to be beneficial in enhancing diabetic healing (23). To provide a direct response to this question, additional research is required.

It is important to note that the functional role that iron plays in the process of wound healing has not been investigated in fully invitro. Lactoferrin is an iron-binding glycoprotein that is released from glandular epithelial cells. Recent research on lactoferrin has focused on the role that it plays in encouraging cutaneous wound healing by boosting the early inflammatory phase, as well as cell proliferation and migration. Using an in vitro model of wound contraction, Aoki et al. (24) discovered that lactoferrin increased fibroblast-mediated collagen gel contraction. This was confirmed to be the case.

In-vivo Studies Investigating the Impact of Iron Chelators on the Healing of Cutaneous Wounds

There is a large amount of variation in the structure of iron chelators, as well as their mechanisms of action and the applications that they are used for. Deferoxamine is the iron chelator that is used to treat iron overload more frequently than any other, as seen in Table 1. In experiments that used a wide array of wound healing models, researchers tried out a number of different iron chelators.

In the earliest trials of porcine flap necrosis, researchers found that administering deferoxamine through intramuscular injection resulted in a lower percentage of flap necrosis (25). The results of this investigation offered some circumstantial evidence 9/21 indicating that iron chelators may have a beneficial impact on the healing process. Mohammadpur et al. conducted a study on the wound healing process using Wistar rats. The primary focus of the study was on calculating the macroscopic wound area on days 4, 8, and 12. They found that topical deferiprone treatment accelerated macroscopic wound healing more than Kojic acid did, and based on further DPPH scavenging assay, they suggested that this was due to its higher antioxidant and iron chelation abilities. This was supported by the fact that topical deferiprone treatment accelerated wound healing more than Kojic acid did.

Chelation of iron resulted in elevated levels of VEGF and HIF-1, which has a beneficial impact on angiogenesis. In investigations of cutaneous wound healing, the influence of iron chelation on the production of granulation tissue and angiogenesis has not been proven. However, there have been some studies of bone tissue in the setting of fracture healing (25). It has been demonstrated that administering a local injection of deferoxamine can both correct the hypovascularity caused by radiation and augment the vascularity in pathologic fracture repair.

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In addition to this, it has been detailed how iron chelators can be incorporated into innovative wound dressing for the treatment of chronic wounds in humans. According to Wenk and colleagues' research, the amounts of iron in wound fluid are significantly higher in human chronic wounds than in acute wounds. They developed a novel wound dressing based on deferoxamine coupled cellulose, and in vitro assays suggested that this dressing may target iron-driven induction of matrix-degrading metalloproteinase-1 and lipid peroxidation. This dressing was based on the fact that they developed a novel wound dressing based on deferoxamine coupled cellulose. Additionally, Taylor et al. constructed and detailed successful biomechanical tests of deferoxamine coupled polyurethane net substrates that they had developed.

Clinical Studies Investigating the Role of Iron in the Healing of Human Cutaneous Wounds

The strength of wounds has been the primary subject of research conducted on humans with anaemia. In these research, a limited number of patients suffering from a variety of acute surgical diseases were included in case series. In a study conducted by Jonnsson et al. On thirty-three patients undergoing subcutaneous implantation of an ePTFE graft, the researchers found that collagen deposition was directly proportional to wound oxygen tension and measures of perfusion. Despite the fact that the anaemia seen in these patients was not fully described, the researchers concluded that collagen deposition was directly proportional to wound oxygen tension. Anemia was not linked with laparotomy wound dehiscence, according to the findings of a retrospective study conducted by Pavilidis et al on eighty-nine patients. The study was carried out by Pavilidis et al (23). A study conducted by Agrawal P et al (24) on thirty-five normovolaemic anaemic individuals who were undergoing skin grafting indicated that there was no difference in the rate at which the wounds healed when evaluated by the mean split-thickness skin graft take.

Iron deficiency and anaemia have not been shown to have a specific influence on the histological phases of chronic wound healing in any of the human investigations that have been conducted to this day. Studies that were conducted in a clinical setting by our team revealed a correlation between the severity of diabetic foot ulceration (DFU) and a decrease in haemoglobin (Hb). DFU is a complicated illness that is characterised by a slow healing of wounds. More than half of all patients diagnosed with severe DFU have iron deficiency anaemia (IDA) (25). Clinically, the anaemia is difficult to characterise; a considerable proportion of patients have a functional iron deficit (FID), which is brought on by chronic inflammation and the disruption of the normal Hepcidin-mediated iron absorption routes.

Chronic leg ulceration is associated with a dysregulation of the local cutaneous iron homeostasis.

Dysregulation of the local cutaneous iron haemostasis has been linked to chronic inflammatory disorders such as rheumatoid arthritis (RA) and lupus erythematosus. RA is a

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progressive inflammatory autoimmune disease that has systemic effects in addition to its impact on the joints. These systemic symptoms include poor wound healing and the development of ulcers. Inflammation of the synovium is brought on by the release of cytokines, including TNF-alpha, IL-6, and IL-1. The production of acute-phase proteins (such as CRP), which in turn may contribute to the development of dysregulation of iron homeostasis and anaemia, is another systemic effect that is promoted by the production of pro-inflammatory cytokines, which also promote the development of other systemic effects. In point of fact, clinical trials conducted on RA patients have reported both iron deficiency anaemia and anaemia of chronic disease. In patients with rheumatoid arthritis, inflammation drives an upregulation in the expression of iron-related proteins in the duodenum and monocytes. Emerging evidence suggests that IL6 signalling may play a role in rheumatoid arthritis (RA). Tocilizumab was found to improve anaemia, result in a drop in hepcidin/haptoglobin, and result in an increase in iron-binding capacity, according to the research of Isaacs and colleagues.

Rheumatoid arthritis (RA) is a chronic inflammatory disease that can cause leg ulcers in approximately 10% of individuals. In clinical practise, rheumatoid arthritis leg ulcers are frequently related with venous insufficiency, trauma, arterial insufficiency, and very rarely vasculitis. In patients suffering from RA and leg ulceration, additional research is required to investigate the effect of IAD.

Lupus erythematosus is a type of autoimmune disease that can appear in a variety of ways in a patient's body, ranging from a relatively harmless skin condition to a potentially fatal systemic infection (SLE). Although this process is not completely understood, some people develop a skin-limited form of the disease, which can present in a variety of ways, including mouth ulcers. Other patients, however, develop systemic lupus erythematosus as the disease progresses. Exposure to UV radiation is a major external trigger that plays a role in the beginning stages of the activity of skin diseases. It has been demonstrated that photosensitive patients who have cutaneous lesions also have anti-Ro/SSA autoantibodies. [Citation needed] [Citation needed] Antigens such as Ro52 have been shown to be up-regulated in keratinocytes, according to research conducted in vivo (22). It is likely that the release of iron in reaction to UV radiation hinders the function of these antigens, which appear to play a part in the process of negative feedback in response to inflammation. This is something that is of considerable interest.

The Adverse Effects of Iron Deposition on the Local Cutaneous Surface

In the pathophysiology of chronic venous illness, there has been considerable interest in the function that excess iron stored in the skin as haemosiderin may play. [Case in point] [Case in point] (CVD). It is currently believed that the severe alterations in skin (such as lipodermatosclerosis) and leg ulcers that are related with cardiovascular disease take place once iron overload takes place. Erythrocytes that are loaded with iron can leak out of the

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veins when there is high venous pressure, which is characterised by an unusually leaky venous valve. There is an increase in the amount of haemosiderin that has been deposited in the dermis. The process of erythrophagocytosis causes iron to be loaded onto macrophages, which leads to unrestricted activation of the pro-inflammatory macrophage response. The production of reactive oxygen species (ROS) results in a chain reaction of damaging processes and an increase in the level of oxidative stress. There is also an inflammatory reaction caused by tumour necrosis factor alpha (TNF-) and interleukin-6 (IL-6), which causes venous leg ulcers to repeatedly recur (VLU). Matrix metalloproteinase (MMP) activation and fibroblast senescence are both necessary steps in the development of dermal fibrosis. Recent research conducted by Sindrilaru and colleagues (23) has uncovered a group of iron-overloaded inflammatory M1-like macrophages. These macrophages are thought to have a role in the development of cardiovascular disease.

Following the formation of a serum haptoglobin/hemoglobin complex as a result of haemoglobin being released from extravasated erythrocytes, the complex is then taken up by macrophages following the overexpression of the hemoglobinhaptoglobin receptor CD163. Continuous uptake of haemoglobin is hypothesised to be the origin of high intracellular concentrations of heme-iron that stimulate unrestrained pro-inflammatory macrophage activation in CD163high macrophages. This activation is caused by macrophages that have a high level of the CD163 antigen. As a result of an increase in systemic or local hepcidin expression, which causes a reduction in ferroportin, an iron efflux protein, and ultimately results in intracellular iron accumulation, the iron content of macrophages can be raised to an even higher level during an inflammatory response. Individuals may also have a hereditary predisposition to develop cardiovascular disease due to an inability to combat an excess of iron in the skin (45). Studies have demonstrated that frequent haemochromatosis gene variants such as the C282Y mutation roughly seven times enhance the risk of ulceration in patients with chronic venous illness.

Hereditary haemochromatosis is characterised by an increase in plasma iron level that exceeds the iron binding capability of transferrin, despite the fact that erythropoiesis is proceeding normally. Studies that used quantitative nuclear microscopy to quantify the concentration of iron in the epidermis (which is an easily accessible tissue) demonstrated that the levels of iron in the skin reflect the amount of iron that is stored in the liver. It is interesting to note that this method has been presented as a therapeutic tool to enable more informed judgements regarding the appropriate times to begin, change, or discontinue phlebotomy therapy. In both cardiovascular disease and hereditary haemochromatosis, parenchymal iron deposition causes activation of metalloproteinases, which in turn leads to fibrosis in the affected tissue.

Hereditary haemochromotosis has also been utilised in research examining how iron contributes to the maturation process. When administered topically, iron chelators help normal skin age in a way that is considered to be "successful." This means that a relative iron

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overload may potentially have a negative impact on normal skin ageing. Ulceration of the legs is one of the most significant contributors to morbidity in sickle cell anaemia (SCA). Haemoglobin levels that are below 6 g/dL, decreased levels of foetal haemoglobin, haemolysis, elevated lactate dehydrogenase, infections, and inflammation are all known to be risk factors for the development of leg ulcers in SCA patients. It is quite likely that the adverse consequences of excessive local cutaneous or macrophage iron deposition play major roles in poor wound healing in SCA as well as in other illnesses that cause haemolytic anaemia (such as hereditary spherocytosis, thalassemias, and other haemoglobinopathies).

CONCLUSION:

Over the course of the past few years, there has been some progress made in our understanding of iron in the skin and iron shortage in the healing of cutaneous wounds. Studies on the pathogenesis of cardiovascular disease have made it abundantly evident that high levels of iron in macrophages might lead to unrestricted activation of proinflammatory macrophages.

Furthermore, when serum hepcidin levels are elevated in situations of iron deficiency or anaemia of inflammation, the interaction between hepcidin and ferroportin can lead to increased iron concentration in cells, particularly macrophage. This may potentially have a negative effect on wound healing. It is likely that one of the latter stages of wound healing, such as remodelling, will be affected by iron deficiency even in the absence of inflammation. Priority should be given to the conduct of additional in-depth scientific research into both the underlying pathophysiological mechanisms and the role of local cutaneous iron in disorders associated with iron overload and iron shortage. Iron can be used as a possible therapeutic target in the skin through the use of topical iron chelators and other new pharmacological agents, as well as in delayed cutaneous wound healing through the treatment of iron deficiency.

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