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Review

The importance of oxygen release in diabetic foot ulcer wounds

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Abstract: Oxygen is the essential element required for proper physiological function of cells, tissues and organs within healthy human body. Thanks to its intricate structure, the skin provides a multiprotective barrier against traumatic and non-traumatic injuries, but also a complex and successful self-healing process of the affected tissue. In the particular case of chronic skin wounds, such as diabetic foot ulcer wounds, there is an immediate demand to develop alternative procedures that prevent infection, speed up healing and eliminate any disrupting factor that may interfere with the therapeutic process. Given the importance of oxygen during wound healing cascade, impressive attention was oriented towards the fabrication of oxygen-releasing wound dressings.

Keywords: diabetic foot ulcer, oxygen release/delivery, wound dressing

1. Introduction

An essential factor for normal embryonic development, bone formation, angiogenesis, stem cell function and wound healing is the oxygen concentration within tissues, which is naturally controlled by intrinsic biological processes of the human body. Given the fact that oxygen is a vital element during physiological function and differentiation of cells and tissue, its presence during all stages of wound healing and regeneration of injured tissue is of critical importance [1]. The beneficial activity of oxygen in wound healing process relies on the following specific events: (i) stimulation of collagen synthesis by supporting re-epithelialization, which occurs through the proliferation and migration of fibroblasts and keratinocytes (processes mediated and regulated by local cytokines and growth factors); and (ii) induction of angiogenesis, which depends on endothelial activation, but also on proliferation and migration of dermal and epidermal cells within wound bed [2, 3].

In the absence of oxygen, the function of the injured tissue will be compromised and the healing-related neovascularization will be critically delayed or impaired [4].

It is worth mentioning that significant efforts were directed towards the development and implementation of unconventional oxygen-based

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therapies for wounds care management. Even if the reported data are undoubtedly of clinical importance, there were also reported some negative results, most of them being related to hyperoxygenated wounds [2, 5].

There is big evidence regarding oxygen-enriched and oxygen-releasing wound dressings, which provide decreased inflammation and better wound perfusion that automatically stimulate an accelerated wound healing. In this case, the oxygen molecules are delivered in a targeted and continuous manner to the affected skin site. Additionally, such oxygen dressings represent effective and more comfortable therapeutic method for patients, in comparison with other oxygen therapies [6].

15% of the patients that are affected by diabetes also suffer from associated foot ulcers, which represent a severe complication that impacts the patient's quality of life, but also a great burden for healthcare services. The diabetic foot ulcer is a complex disease that occurs when several risk factors overlap with the persistent hyperglycemic state of body. Etiologic factors related to foot complications in diabetic patients include peripheral neuropathy, impaired immune system and peripheral vascular disease [7, 8]. Even if there are strategies to prevent the occurrence of diabetic foot ulcer wounds, there is an immediate need to develop and implement clinical alternatives for diabetes-associated complications.

2. Wound management

It is known that natural healing of skin wounds is an extremely complex process that depends on several interconnected factors that induces restoration of the injured skin, recovery of the barrier function of skin and support for the healing process. These processes generally occur in acute skin wounds, but these phases are disrupted in the case of chronic wounds, particularly in diabetes-associated wounds[6, 9].

Known as the largest organ of the human body, the skin provides extensive protection for internal structures and represents a natural barrier against a wide variety of external stimuli. There are no blood vessels in the epidermis and the stratum corneum (consisting in terminally differentiated keratinocytes) acts as a mechanical barrier against exogenous substances and microorganisms [10, 11]. When microbial invasion succeeds in penetrating the natural defense layer, skin and adjacent soft tissue infections occur [12]. In terms of clinical severity levels, soft tissue infections can be superficial and relatively mild (e.g. impetigo) or deep and severe (e.g. necrotizing fasciitis) [13].

The technological progress and the modern healthcare practice enable impressive progress regarding new and effective alternatives for skin wounds healing and most of them rely on the natural-occurring physiological mechanism. It is worth mentioning that wounds management represents a huge business on the medical market. Currently, the sale of wound care products exceeds US$ 15 billion, and more special products for scars treatment another US$ 12 billion [14].

One of the most important conditions in wounds treatment is the restoration of macro and microcirculation [15]. It is confirmed that one of the most readily available, fast and efficient strategy implied for this purpose is the oxygen supply, which promotes and support the reconstruction of connective tissue and the reactivation of intrinsic resistance against pathogenic cells. In the case of patients who experience difficulties in wounds healing (such as diabetic foot ulcer and peripheral arterial occlusive disease) , a practical solution is the sustained supply of oxygen at the wound site [16].

Unfortunately, non-healing wounds represent a critical problem for nowadays healthcare system. There is a chance that 1-1.5% of the general population suffered, at some point in life, a wound that couldn't be normally healed.

3. Wound care and dressings

Wound healing has always been an area of concern for medical community, but the nowadays interest for this topic is significantly amplified, because of the increased mortality rate associated with chronic wounds. Several factors are important in the effective treatment of wounds, including the debridement stage that consists in removing the non-viable or infected tissue from wound environment [17]. In chronic wounds, it is recommended to perform the debridement process as early as possible, by using either non-selective (surgical and mechanical debridement) or selective (autolytic, enzymatic and biodebridement) methods. These mechanisms consist in cleaning wound debrides and exposing healthy wound bed tissue that further stimulate proliferation and migration of epithelial cells, repopulation of wound bed and formation of granulation tissue [18].

In terms of autolytic debridement, this mechanism refers to self-stimulation of endogenous biomolecules within wound exudate (enzymes, growth factors and cytokines) that act during fibrin degradation induced in a moist environment (as in the wound or generated by some wound care products) [19]. In the case of enzymatic debridement, ointments, gels and dressings containing debriding enzymes are used to remove the necrotic or infected tissues [20]. More recent methods for selective debridement of chronic wounds include larvae or maggots debridement, also known as biosurgical debridement [21, 22]. This unconventional method represents a rapid, efficient and attractive method for debrides cleaning, consisting in concurrent surgical and enzymatic debridement accompanied by removal of pathogens; all these specific actions provides a faster healing process [23].

When fabricating a dressing for chronic wound, it is essential to (i) provide protection against contamination and colonization of pathogenic microorganisms; and (ii) to support the healing process. A relevant example is represented by moisture occlusive dressings that are used in the inflammatory phase of wound healing and provide a low-oxygen tension environment, but also participate in increasing the rate of re-epithelialization [24]. Moreover, if a small amount of exudate is maintained at the wound site, then autolytic debridement begins healing process occurs, subsequently.

By considering the available commercial dressings, it was concluded that films with partial permeability for air and water vapor and low adherent properties (preventing thus the adhesion and migration of microbial cells) are the most commonly used dressings for chronic wounds healing.

Hydrogels represent the most versatile materials used in wound healing strategies, being characterized by highly hydrophilic molecular networks, adequate flexibility, similarity with the physiological water content of skin tissue, impressive swelling capacity and stimuli-responsive behavior for pH, temperature and ionic strength [3]. By their highly hydrophilic nature, hydrogels and hydrocolloids have the ability to absorb a substantial amount of exudate, in relation to their size, and to maintain a moist wound bed environment. Hydrocolloids differ from hydrogels through their increased air impermeability and prolonged capacity to provide active support for wounds. A very promising material used in hydrogel formulations for wound dressings is natural-derived alginate, especially used for excessive exudative wounds thanks to its ability to absorb a large amount of fluid [25]. Promising results in chronic wounds care are also associated with other polysaccharide-based hydrogels, such as chitosan [26], hyaluronan [27] and dextran [28]. Similar properties are found in the case of foams that can be applied to wounds with medium exudates [29, 30]. An attractive approach in modern wound care is the combination between healing dressings and antimicrobial agents. Superior results were reported when embedding antimicrobials within different wound dressings, including commercial antibiotics, natural-derived antimicrobial agents and metal or oxide nanoparticles [31, 32]. Based on the currently available data, it can be certainly stated that antimicrobial dressings have beneficial effects in

fighting pathogens and combating microbial biofilms in chronic ulcers wounds [33, 34].

4. Wound healing process

After a wound is produced to the skin, a series of innate systems (immune, cellular and vascular) quickly activate at the affected site to heal the wound and restore the physiological function of skin tissue [35]. Following the occurrence of a skin wound, the body's structures activate the natural healing process, which starts with hemostasis and inflammation stages, followed by cellular proliferation and tissue remodelling phases. During this complex process, different immune cells, blood platelets, immunomodulatory and anti-inflammatory cytokines, chemokines, growth factors and nutrients are delivered to the affected skin tissue, their activity being correlated and thoroughly regulated by the metabolic requirements [36].

The first physiological event that follows after the skin tissue injury is hemostasis, initiated by coagulation factors. Subsequently, the inflammatory phase of healing process occurs, which promotes the local elimination of pathogens and external materials and acts against the expansion of the affected area. Neutrophils and monocytes, representing the first and second inflammatory responders, respectively, reach the affected site by enhanced vascular permeability. Also, this phase of wound healing is based on complex and finely regulated interactions of distinctive cytokines (signaling small proteins secreted by affected skin cells and blood platelets from previous phase) and growth factors, that stimulate the chemotaxis of monocytes to the wound site and promote the differentiation of monocytes into macrophages [37]. These macrophages not only phagocyte exogenous agents and remove tissue debrides, but also support the secretion of growth factors and cytokines that encourage cell migration and tissue proliferation. At the end of the inflammatory phase of wound healing (about three days), the proliferative phase follows; it consists in the proliferation and migration of fibroblasts and subsequent production of granulation tissue (enriched with collagen and fibronectin). Simultaneously, endothelial cells migrate from wound edges and rapidly populate the wound bed, forming thus the granular tissue that develops angiogenesis; these two processes generate a generous vascular network that plays a critical role during this very active and rapid healing stage. Finally, about 2-3 weeks after skin wound occurrence, the remodelling phase appears in order to regain an ultrastructure that is similar to the initial one (corresponding to healthy skin tissue). During this stage, collagen type is locally replaced as to correspond to the unwounded tissue, and the once-injured area enters a maturation state that finally leads to the restoration of a normal and healthy structure and function of skin tissue. Withal, the vascular network returns to its initial activity through a rapid process [38].

Although these phases concretely sustain the wound healing process, yet it is difficult to reach the normal condition of initial skin tissue. An important requirement that must be considered for a more successful healing of the affected tissue is the nutrition of the lesions (systemic administration or macrominerals, vitamins and proteins), but especially oxygen supplementation. Wound healing depends on the level of oxygen, providing beneficial interactions of numerous cytokines, supporting cell proliferation, stimulation angiogenesis and collagen synthesis. It has been shown that acute and non-complicated wounds need at least 2 mmHg oxygen tensions for healing. Chronic and complicated skin wounds generally undergo hypoxia, which results in delayed healing process, increased amount of wound necrotic tissue and impaired ability to combat microbial contamination [39, 40]. Besides the requirements of wound microenvironment (nutrition, oxygenation, vascularization), other external factors must be considered during the healing of chronic wounds, including moisture, temperature and pressure [41].

Special attention should be given in the case of wounds that occur in vascular compromised patients, suffering from peripheral vascular disease or circulatory complications associated with other systemic diseases (such as diabetes).

5. Diabetic foot ulcer wounds

A main concern of diabetes management is the treatment of associated chronic wounds. A statistical analysis of the USA population revealed a concerning and increasing in the number cases of diabetes (approximately 20 million); by 2030, the cases of diabetic patients are expected to double. Diabetic foot ulcer occurs in 15% of these patients and most clinical cases end up with amputation surgery. A glycemic level analysis may have a significant effect in healing the affected tissue by adequate glycemic control in a diabetic patient. It is well known that controlling glycemic levels is a challenge; but the adequate control of glycemia in diabetic patients have benefits not only on the patient's quality of life, but also on the treatment of diabetes-associated chronic wounds [42, 43].

Foot ulceration represents moderate to severe complication responsible for the increasing mortality in diabetic patients. In combination with mechanical deformity of the foot, there are several risk factors responsible for the occurrence of diabetic ulcers, , such as peripheral vascular disease, peripheral neuropathy and impaired immunodeficiency (which can further determine the occurrence of opportunistic infections) [44, 45]. Ulceration of diabetic foot significantly impair the already delicate healthcare status of the patient, but also affects individual lifestyle; therefore, special care is required in the management of diabetes-associated complications General statistics based on foot amputation surgery evidence that more than 60% of these procedures are done in patients with diabetic foot ulcer and the main factor leading to this tragic and final action is represented by infection-complicated wounds [46]. An extensive study in diabetic foot ulcer patients has shown that the risk of amputation increases by up to 50% when ulcerative infections overlay [47]. In order to properly control and manage the diabetic wounds, it is necessary to take into consideration the following: precise diagnosis, specific lesion identification, appropriate choice for bacterial testing, standardized options for antimicrobial therapy and precise consideration for protocols of wound care [46].

Healing (or at least keeping certain factors under control) consists in control of the infection, surgical debriding and, in some cases, vascular reconstruction, thus avoiding amputation [48, 49].

5.1. Diabetic foot infection

There are several pathological processes that can occur in diabetic foot, which can affect the skin, muscles, bones, even nerves and blood vessels. Foot infections are usually initiated in a ruptured skin fold or in an ulcerative area. The infection is best described as the process of invasion of microorganisms followed by their multiplication at the host tissue level, which causes the specific inflammatory response. In the case of a diabetic patient, infection associated with foot ulcer wounds can occur within the associated local tissues, such as soft tissue or even bone tissue [50].

5.2. Wound dressings

A suitable method to prevent infection-associated wounds consists in using dressings that exhibit beneficial properties for structural and functional restoration of the injured tissue, such as barrier activity by providing protection against exogenous agents (including contaminants and microorganisms) and bioactive activity by owing the ability to absorb exudate caused by the ulcerative wound. A wide variety of dressings are commercially available nowadays, their types and specific properties depending on the localization of wound, nature and class of material, dimensions, embedded or attached therapeutic agents, topical administration method, ability to rapidly and successfully support and promote the healing process. It is worth mentioning that the modern management of wounds relies on innovative dressings, which provide the suitable compositional, structural, molecular and biofunctional features for wound healing [51]. Examples of commercially available dressings: Aquacel Ag hydrofiber, Biatain Ag, Silvercel, Poly skin II, Cutinova Gel, 2nd skin Flexderm, Debrisan, Fibracol®, ActiFoam etc [52-54].

6. Importance of oxygen release in wounds treatment

Oxygen in an essential element required during the healing process of acute, chronic and surgical wounds. Oxygen supply within the injured wound promotes increased energy production and thus stimulates collagen production, cell proliferation, re-epithelialization and fighting against bacterial activity [23].

The oxygen pressure (pO_2) below the critical oxygen level (known as hypoxic threshold) is generally associates with a deficitary healing process. Thus, in order to provide the wound proper conditions to heal, it is desired to maintain a sufficient quantity of molecular oxygen to within the wound area. When O_2 consumption is more substantial than molecular oxygen release, the hypoxia process happens. The occurrence of local wound hypoxia is related to the reduced level of circulating blood due to narrowed vessels or / and to the modification of hemoglobin due to hyperglycemia [55, 56].

Besides oxygenation, which is critical during the healing process of skin wounds, another beneficial effect related to oxygen supply is supporting the production of reactive oxygen species that concurrently have bacteriotoxic effect and stimulate angiogenesis. Due to the fact that chronic wounds are characterized by local hypoxia and accompanied by reduced bactericidal activity of the leukocytes, various therapies involving oxygen therapy have been developed over time. These unconventional, but successful strategies to manage chronic wounds consists in local delivery or / and release of oxygen by using oxygen-releasing dressings or topical oxygen therapy [23, 57].

6.1. Oxygen intake through wound healing

The energy requirement for normal function of the body is provided by oxygen consumption during aerobic respiration. In the case of skin defects, oxygen is the most important and rapid factor required for optimal healing, contributing to the structural and functional restoration and regeneration of the affected tissue. Oxygen consumption is necessary to activate the transcription factors that support and promote angiogenesis factors. Oxygen supply is needed throughout the wound healing process, being beneficial for the restoration of connective tissue, proliferation of fibroblasts, maturation of collagen fibers within the newly-formed tissue and proficient host response to infectious processes [58, 59].

6.2. Oxygen delivery in wounds

The presence and amount of oxygen in the wound, evaluated by monitoring the pO_2, depend on its contribution in the circulating blood and tissue around the affected site. Besides circulatory diseases which hinder proper oxygen supply, microbial biofilm also impairs the local levels of oxygen. Oxygen level is much faster and in higher amounts consumed due to metabolic activity occurred in the treatment of wounds, so it will be overall reduced in tissue [60].

The use of oxygen-enriched or oxygen-generating dressings, which can be considered controlled and targeted release systems, is beneficial for promoting a successful wound healing process; additionally, these materials are highly safe for the human body, since they do not produce any toxic effect [60].

The correct wound healing is well sustained by oxygen therapy that contributes to neovascularization, extracellular matrix synthesis, metabolic support and, most important, inhibition of microbial activity. In order to provide maximal efficiency, the hyperoxygenation therapy generally implies costly procedures and difficult lifestyle protocols to follow. In order to provide oxygen supplementation without affecting the patient's convenience, genuine and multifunctional dressings can successfully be used. Several strategies can be used to generate supplemental oxygen to skin wounds, including oxygen gas flow devices, topical oxygen therapy and oxygenating dressings [61].

7. Conclusions

Wounds in skin or adjacent tissues can be produced through cuttings, burns or other traumas. By using the proper wound dressing, the wound surface is protected against external contaminants and microbial invasion and, at the same time, the healing process is promoted.

Oxygen represents one of the most important factors involved in wound healing and fighting against opportunistic infections. It was reported that oxygen-releasing dressings reduce inflammation and provide better molecular and cellular activity at the wound site, stimulating thus an enhanced wound healing process. In addition to other oxygen therapies employed in chronic wounds management, oxygen-releasing dressings are more accessible and convenient to any patient in need of specialized care. Such particular wound dressings offer many benefits, including targeted local oxygen therapy that allows patients to properly receive the necessary treatment, in an inexpensive and comfortable manner.

Given the beneficial implications of oxygen in skin wounds management, specific formulations are commercially available, either as oxygen-releasing dressings or as oxygen-generating hydrogels.

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Conflicts of Interest

The authors declare no conflict of interest.

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