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Tissue repair under the influence of plasma jet and other biomodulator therapies - state of the art

Reparação tecidual sob influência do jato de plasma e outras terapias biomoduladoras - estado da arte

Reparación de tejidos bajo la influencia del chorro de plasma y otras terapias biomoduladoras - estado del arte

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Abstract

Tissue repair process consists in a complex and dynamic event straightly linked to tissues self-regeneration capability. In that context, it may also occur total or partial replacement of the original tissues through an extracellular matrix with significant collagen and elastin expression that results in fibroplasia. Aiming to optimizing the repair, it has been used some resources able to biomodulate the action of different kinds of tissue cells such as laser photobiomodulation (LP), light emitting diodes (LEDs), ozone therapy and plasma jet. This narrative literature review aims to describe the different phases of tissue repair and discuss about biomodulator therapies commonly applied to stimulate that process. Manuscripts discussing the proposal theme, which have been fully available were selected from Pubmed, Embase, Cochrane and Scielo database. The manuscripts must be written in English or Portuguese language, according to the exclusion and inclusion criteria designed for that study. Sixty manuscripts were selected. It may be noticed that biomodulator therapies have been used in health areas. However, studies evaluating the influence of plasma jet on tissue repair are still scarce. Preliminary results from such studies suggest that plasma jet therapy may perform important antiinflammatory, analgesic and biostimulating effects.
Keywords: Wound healing; Laser photobiomodulation; Ozone therapy; Plasma skin regeneration.

Resumo

O processo de reparo tecidual consiste em um evento complexo e dinâmico diretamente ligado à capacidade de autorregeneração dos tecidos. Nesse contexto, também pode ocorrer à substituição total ou parcial dos tecidos originais por meio de uma matriz extracelular com expressão significativa de colágeno e elastina que resulta em fibroplasia. Com o objetivo de otimizar o reparo, foram utilizados alguns recursos capazes de biomodular a ação de diferentes tipos de células teciduais como a fotobiomodulação a laser (LP), diodos emissores de luz (LEDs), ozonoterapia e jato de plasma. Esta revisão narrativa da literatura tem como objetivo descrever as diferentes fases do reparo tecidual e discutir sobre as terapias biomoduladoras comumente aplicadas para estimular esse processo. Os

manuscritos que discutiam o tema da proposta, disponíveis na íntegra, foram selecionados nas bases de dados Pubmed, Embase, Cochrane e Scielo. Os manuscritos devem ser redigidos em língua inglesa ou portuguesa, de acordo com os critérios de exclusão e inclusão elaborados para aquele estudo. Sessenta foram selecionados. Pode-se perceber que as terapias biomoduladoras têm sido utilizadas na área da saúde. No entanto, estudos avaliando a influência do jato de plasma no reparo tecidual ainda são escassos. Resultados preliminares de tais estudos sugerem que a terapia com jato de plasma pode exercer importantes efeitos anti-inflamatórios, analgésicos e bioestimulantes.
Palavras-chave: Cicatrização; Terapia com luz de baixa intensidade; Ozonioterapia; Regeneração da pele por plasma.

Resumen
El proceso de reparación tisular consiste en un evento complejo y dinámico directamente relacionado con la capacidad del tejido para regenerarse. En este contexto, el reemplazo total o parcial de los tejidos originales también puede ocurrir a través de una matriz extracelular con expresión significativa de colágeno y elastina, lo que resulta en fibroplasia. Para optimizar la reparación se utilizaron algunos recursos capaces de biomodular la acción de diferentes tipos de células tisulares, como fotobiomodulación láser (LP), diodos emisores de luz (LEDs), ozonoterapia y chorro de plasma. Esta revisión narrativa de la literatura tiene como objetivo describir las diferentes fases de la reparación tisular y discutir las terapias biomoduladoras comúnmente aplicadas para estimular este proceso. Los manuscritos que discutieron el tema de la propuesta, disponibles en su totalidad, fueron seleccionados de las bases de datos Pubmed, Embase, Cochrane y Scielo. Los manuscritos deben estar escritos en inglés o portugués, de acuerdo con los criterios de exclusión e inclusión desarrollados para ese estudio. Sesenta fueron seleccionados. Se puede observar que en el área de la salud se han utilizado terapias biomoduladoras. Sin embargo, los estudios que evalúan la influencia del chorro de plasma en la reparación de tejidos son aún escasos. Los resultados preliminares de tales estudios sugieren que la terapia con chorro de plasma puede ejercer importantes efectos antiinflamatorios, analgésicos y bioestimulantes.
Palabras clave: Cicatrizacion de heredas; Terapia por luz de baja intensidade; Ozonoterapía; Regeneracíon de la piel con plasma.

1. Introduction

Wounds are characterized by the occurrence of a damage or loss of tissue integrity which change the homeostasis in lesion microenvironment. Organisms' response to that damage triggers a relevant biological process represented by the activation of plasmatic cascades like coagulation, fibrinolytic, complement system and kinins. Usually, these events contribute to the tissue regenaration. Depending on the time, cell components that predominate in repair and the appearance of symptoms and signals, tissue lesions may be classified as acute or chronic (Cheng et al., 2018; Velnar et al.,2009).

During wound healing, it has hugely been documented in literature the unfolding of a series of biological events that include hemostasis, inflammation, neo-angiogenesis, re-epithelization and remodeling of the newly-formed extracellular matrix. At the hemostasis phase, there is an increasing platelet activation and clot formation with release of pro-inflammatory cytokines by defense cells that eventually stay trapped in fibrin network. As long as inflammatory process develops itself, successive waves of white blood cells migration take place represented by the presence of neutrophils, lymphocytes and monocytes that make transmigration in order to eliminate the microorganisms. In an advanced stage of inflammation, it occurs proliferation of fibroblasts and endothelial cells, and trans-differentiation of stem cells present in the extracellular matrix with goal of "repopulation" of the new tissue. Along with these events, epithelial, epidermal or mucosal cells start their proliferation and migration. Regardless of final clinical aspect of the lesion, matrix remodeling will keep for days, months or even years (Bekeschus et al., 2021; Cui et al., 2020).

Usually, lesion repair lasts about four weeks, but there are situations where this process is delayed or incomplete due to local and systemic factors which may interfere in the way of the mentioned events. It ends up in the wound chronification. Additionally, presence of infection at the wound site and clinical conditions that result in tissue hypoxia are some examples of these retarding factors (Velnar et al., 2009).

It is estimated that a lot of money has been globally applied to treat wounds that have compromised healing, that include decubitus ulcers which attacks majority bedridden individuals and causes pain; delay in recovery time, increase in infection risk, and complications from the long-lasting hospitalization. These conditions also impact on patients quality life (Fernandes & Caliri, 2000; Blanes et al., 2004). In front of that scenario, biomodulator therapies are able to modulate tissue repair because of their anti-inflammatory and analgesic effects, besides cellular and molecular signaling (Muller et al., 2007). Resources such as laser photobiomodulation (LP), light emitting diodes (LEDs), ozone therapy and plasma jet have progressively been used aiming to promote the achievement of better healing pattern not only by the clinical side of view, but also from the histological one.

This narrative literature review aimed to highlight the biological processes that define the different phases of tissue repair and, briefly, to describe some therapies which modulate it, mainly, plasma jet utilization. The plasma jet will be more emphasized due to the fact of there are few studies which indicate such therapy for wound healing.

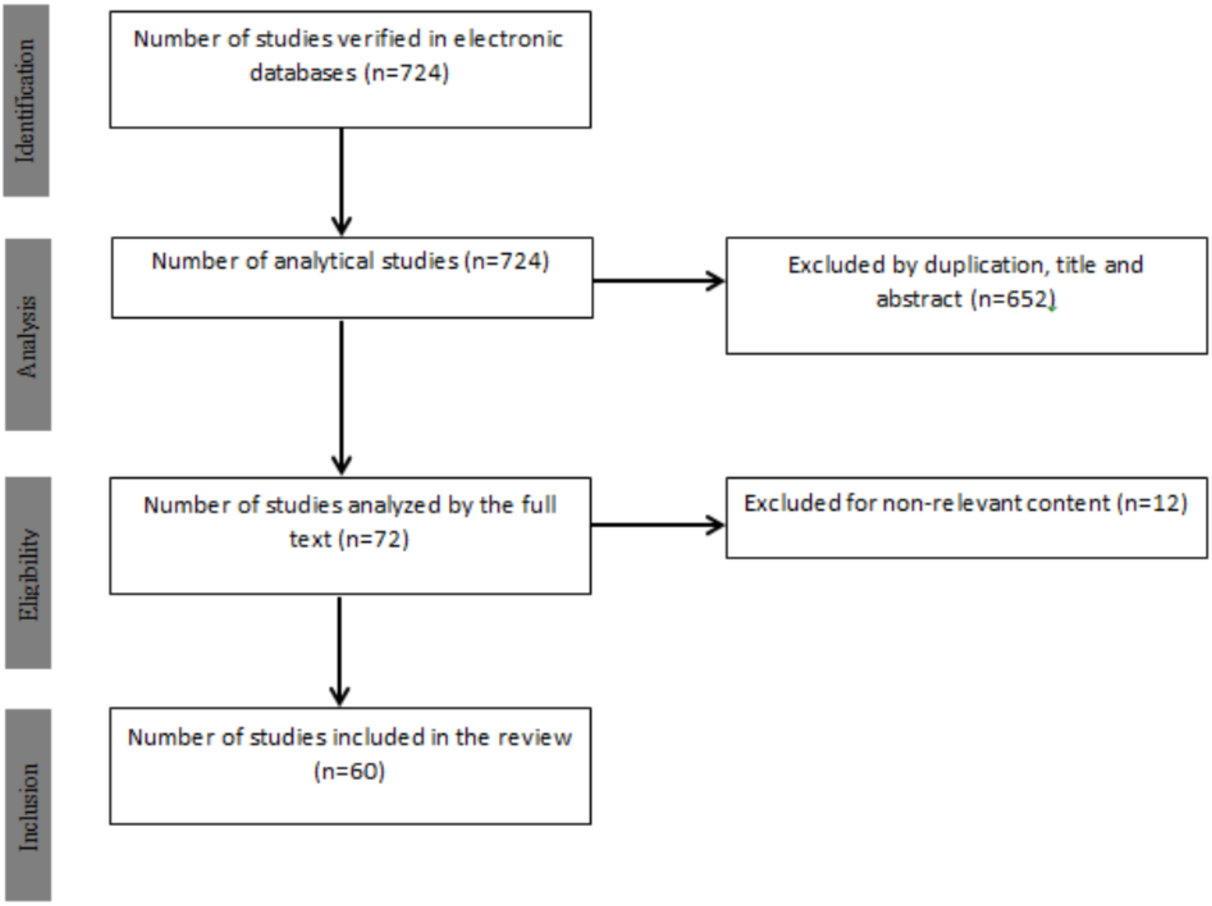
2. Material and Methods

This study was designed as a narrative literature review. The literature search was undertaken at four electronic databases: Pubmed, Embase, Cochrane and Scielo. The descriptors obtained by DeCS/MeSH that were used included "Wound Healing", "Laser Photobiomodulation", "Ozone therapy" and "Plasma Skin Regeneration". In addition, the Boolean descriptors AND/OR were inserted the search. From the results, a refinement was carried out in the literature search that aimed to identify only studies which approach tissue repair and influence of biomodulator therapies on it, particularly those which approached using plasma jet.

Inclusion criteria to the selection of scientific manuscripts were: fully text available in Portuguese or English without restrictions regarding year of publication and kind of study. That last point regards to the lack of studies about the subject. Moreover, manuscripts should discuss about tissue repair and/or biomodulator therapies already described in the literature. Then, all manuscripts which did not approach the proposed subject were excluded. A total of 60 manuscripts were selected from database and used at this review.

At the beginning of the search, a total of 724 publications were found. After reading the title and abstract, 652 studies were removed, due to duplication or not meeting the reading criteria for publications. A total of 72 articles were full read. Twelve studies were excluded because they did not presented relevant content. Finally, a total of 60 studies were included in the review. The selection of studies is reproduced in the a flowchart (Figure 1).

Figure 1: Process of identification and inclusion of studies. Source: Authors.



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3. Result and Discussion

3.1 Tissue Repair – a complex biological event

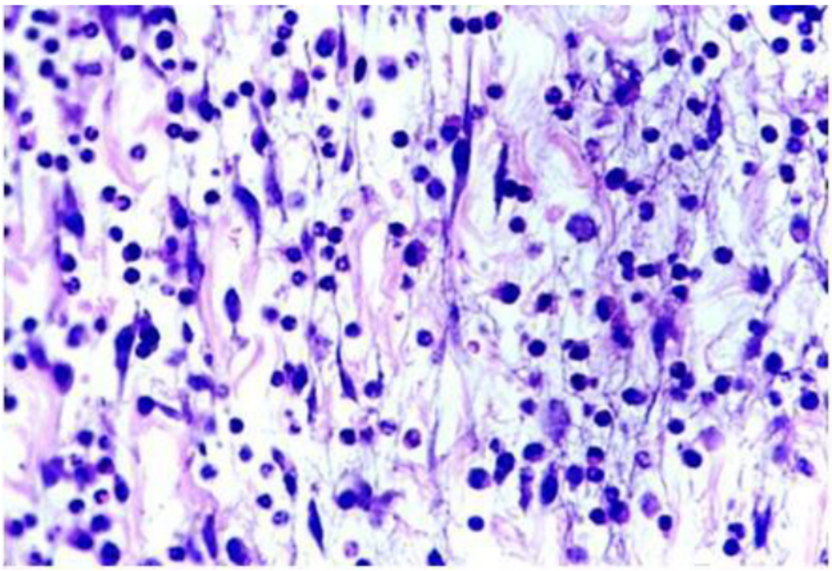
Tissue repair process is straightly linked to the self-regeneration capability of a certain tissue and can occur in two ways. The first one is presented by the tissue regeneration which allows an effective recovery in the morpho-functional activity of the parenchymal cells. With regard to the second way, it evolves healing or repair by replacement, process that is defined by a partial or full replacement of the original parenchymal with connective matrix tissue rich in collagen and elastin which results in fibroplasia. Generally, these biological events are characterized for phases that overlap in order to reestablish tissues homeostasis (Balbino et al., 2005; Isaac et al., 2010).

Just after tissue damage, some immediate effects are triggered. Initially, it takes place a quick vasoconstriction that represents a neurogenic mechanism of defense aiming to minimize blood loss for the extravascular space (Toriseva & Kähäri, 2009). The endothelial cells alter their morphology and reorganize their cytoskeleton in a certain way that allow plasma and blood cells leakage (Oliveira & Dias, 2012). Simultaneously, a physiological reaction called hemostasis triggers itself in the tissue addressing to restore vascular integrity and stop bleeding. At this stage, the extravasated blood is clotted, in other words, the area is recovered by a primary fibrin network, a protein that contains the hemorrhage since working along with platelets. Then, the proteolysis and plasmatic protein activation, which integrate blood coagulation cascade, will result in the clot formation. This clot, in addition to favoring the reduction of wound edges and blood loss, also protects the tissue from viral microorganisms as well as stimulates synthesis of a provisory matrix at the wound bed (Dário, 2008; Arnold, 2006).

Vascular changes that happen in the tissue, especially in the venous vessels contribute to the establishment of cardinal signs in the primary inflammatory phase. These changes have been described by Cornelius Celsius and include flushing, tumor, heat and pain. Furthermore, some changes in physical-chemical composition at the injured microenvironment, occur. They include low O_2 tension, reduction of pH and nitrogen and reactive oxygen species (ROS) generation. Such reactions trigger a complex cascade signaling and end up activating different cellular populations evolved in tissue repair, besides inducing the tissue damage which results in impairment of tissue functional activity (Balbino et al., 2005).

Acute inflammatory phase that dominates the first 48 hours after initial damage, results in significant hemodynamic modifications with a predominance of exudative phenomena (Osted et al., 2016). Then, vasodilation happens, which contributes to leucocytes transmigration responsible for composing the first defense line against the damager agent. Opening new capillary beds promotes a response/answer characterized by edema and hyperemia in the wound bed which are clinically seen by the increase on volume and site temperature, and also erythema. Neutrophils show a huge variety of granules with powerful proteolytic enzymes and represent the first defense line of innate immune response (Figure 2). Their transmigration results in autolysis and heterolysis and also activate other defense cells through releasing chemical mediators, specially ROS (Gonzalez et al., 2016; Dube et al., 2003).

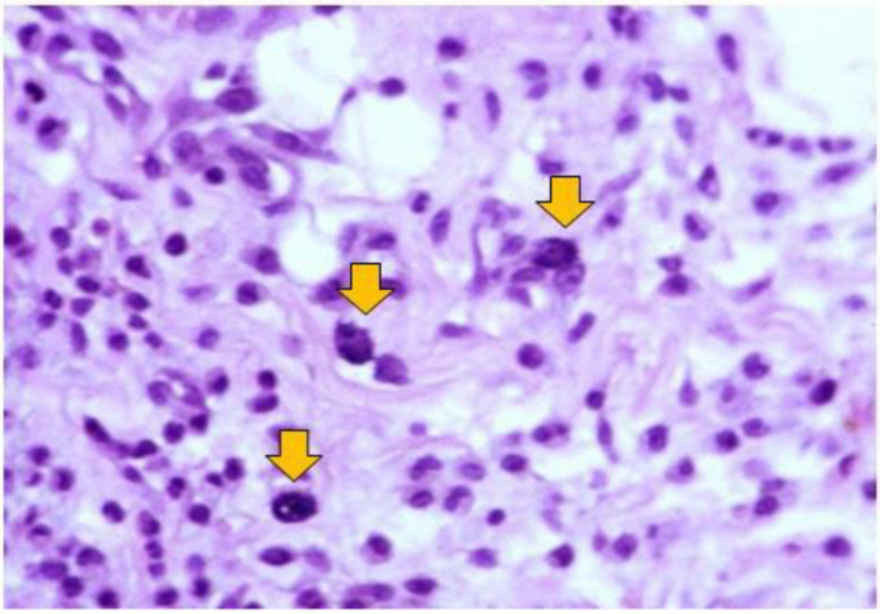
Figure 2. Presence of polymorphonuclear inflammatory infiltrate in connective tissue that evidences innumerous neutrophils which integrate the inflammatory infiltrate. Hematoxylin-eosin, 400X. Source: Authors.



Source: Authors.

Beyond the selective transmigration of white cells, in this initial stage, other cells of conjunctive tissue release and/or synthesize inflammatory chemical mediators which are responsible for the initial vasodilation. An example that illustrates that situation is the degranulation of mastocytes with histamine, serotonin, tryptase and pro-inflammatory cytokines releasing (Pereira et al., 2010) (Figure 3). Mastocytes play an important role in the tissue repair since they synthesize chemical mediators that promote neo-angiogenesis, amplify vasodilation and contribute to the migration of more inflammatory cells at the site of the wound (Correia & Medrado, 2013; Mendonça & Coutinho-Netto, 2009).

Figure 3: Mastocytes (arrow) that show different patterns of cytoplasmatic coloring indicating previous degranulation. Hematoxylin-eosin. Micrography. 400X. Source: Authors.



Source: Authors.

Many chemical mediators started to be synthesized by inflammatory cells and by mastocytes, macrophages and fibroblasts. For example, the platelets activator factor (PAF) induces a vasoconstrictor action in low concentrations, and also brings about an increase of permeability and vasodilation in high concentrations. Furthermore, prostaglandins and leukotrienes derived from arachidonic acid, control blood flow, increase vascular permeability with consequent accumulation of exudate in the connective tissue. Besides, they also stimulate the hypothalamus thermoregulators centers (Bechara & Szabó, 2006).

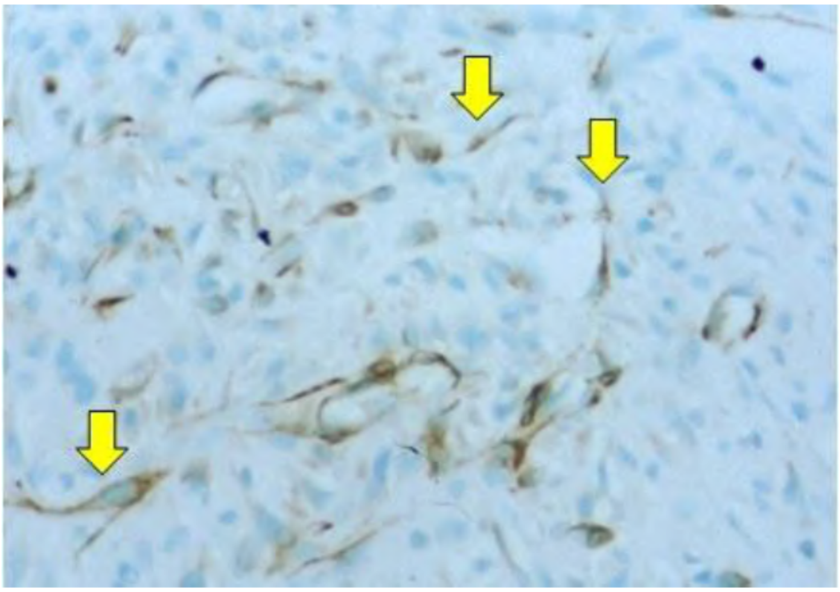
Polymorphonuclear cells make continuous transmigration, and predominate in the inflammatory infiltrate up to 72 hours after damage. Among the main functions from those cells, it is worth to mention the phagocytic ability that make possible to englobe bacteria and other kinds of microorganism, and also promoting their neutralization through an oxidative outbreak. Simultaneously, monomorphonuclear cell infiltrate represented by monocytes and lymphocytes, becomes more prominent in microenvironment. Specially, macrophages which come from monocytes differentiation, act as antigen presenting cells and trigger answers at site and systemic level (Mandelbaum et al., 2003; Lacerda Neto, 2003).

The proliferative phase is marked by neo-angiogenesis, a biological process that promotes an increasing of the vascular network, with the opening of new pre-capillary sphincters. At this time, the conjunctive tissue exhibits a granular appearance and so, is named as granulation tissue. It represents a provisory matrix essentially characterized by vascular proliferation, persistence of monomorphonuclear cells and neo-collagenesis (Mendonça & Coutinho-Netto, 2009). There are growing collagen biosynthesis, wounds contraction and fibroplasia. Gradually, keratinocytes migrate from the damage/lesion surroundings/edges that will contribute to wound closing – the re-epithelization (Osted et al., 2016; Gonzalez et al., 2016; Werner & Grose, 2003).

Usually, proliferative phase takes place from 4 to 12 days after initial biological challenge and is regulated by macrophages and different lymphocyte subpopulations. Growth factors secreted by macrophages such as Transforming Growth Factor Beta (TGF-β) are relevant to stimulate vascular and cellular proliferation as well as the biosynthesis of new compounds of extracellular matrix (Oliveira, 2012; Medeiros & Dantas-Filho, 2016).

The process of neo-angiogenesis that integrate granulation tissue decreases as long as oxygenation and blood flow are restablished[22]. In that context, there is intensive fibroblastic and myofibroblast proliferation. Myofibroblasts are responsible for wound contraction as long as they synthesize collagen fibers and allow a retraction in the damage edges promoting the final closing of the lesion by its smooth muscle alpha actin contractile filaments (Figure 4) (Paganela et al., 2009; Sarandy, 2007; Ramalho et al., 2003).

Figure 4. Presence of fusiform cells (myofibroblasts), (arrows) in the extracellular matrix with positive immunostaining cells for alpha smooth muscle actin, 400X. Source: Authors.



Source: Authors.

In the transition from proliferative to remodeling phase, keratinocytes and fibroblasts migration becomes intensive which results in the re-epithelization and neo-collagenesis, respectively (Figures 5 and 6). The re-epithelization will allow the protection of wound against pathogens invasion and attacks from chemical and physical deleterious agents to tissue formation. It also prevents fluid loss too. This last and the longest phase of wound healing is clinically defined by the attenuation of inflammatory signs such as edema, heat generation and erythema. Although there is a reduction of cellular activity, number of vessels and increase in the tension strength through the organization of collagen fibers. In addition, matrix metalloproteinases (MMPs) action and their respective inhibitors will significantly contribute to the whole healing process (Balbino, 2005; Medeiros & Dantas-Filho., 2016). MMPs are synthesized and expelled by different cell populations, for example, neutrophils, monocytes, macrophages and fibroblast. Such proteolytic enzymes are responsible for extracellular matrix degradation. Along with their action, growth factors promote continuous remodeling of the lesion area. This phase can last for months regardless of final clinical appearance of the scar (Medrado, 2001; Granville et al., 1998; Vieira et al., 2002; de Souza Araújo et al., 2011).

Figure 5. Photomicrograph that shows re-epithelialization (arrow) that takes place bellow the crust (cross) resulting from fibrins denaturation. Hematoxylin-eosin, 100X. Source: Authors.

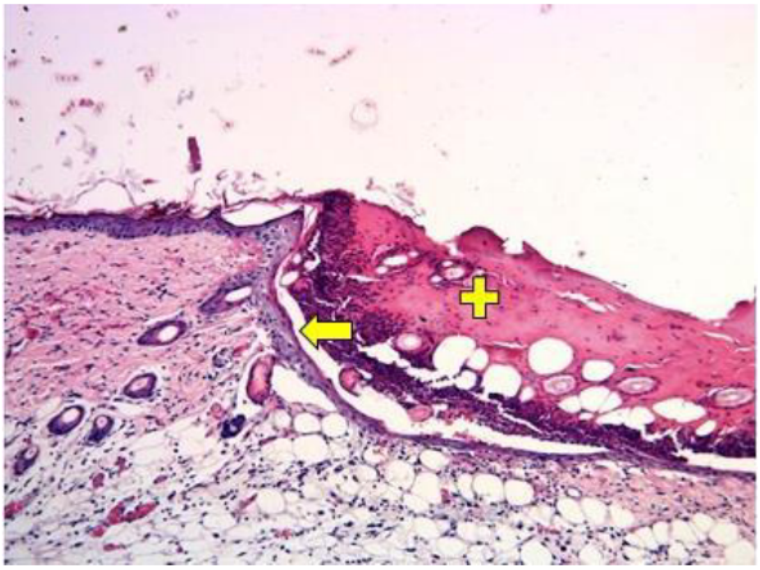


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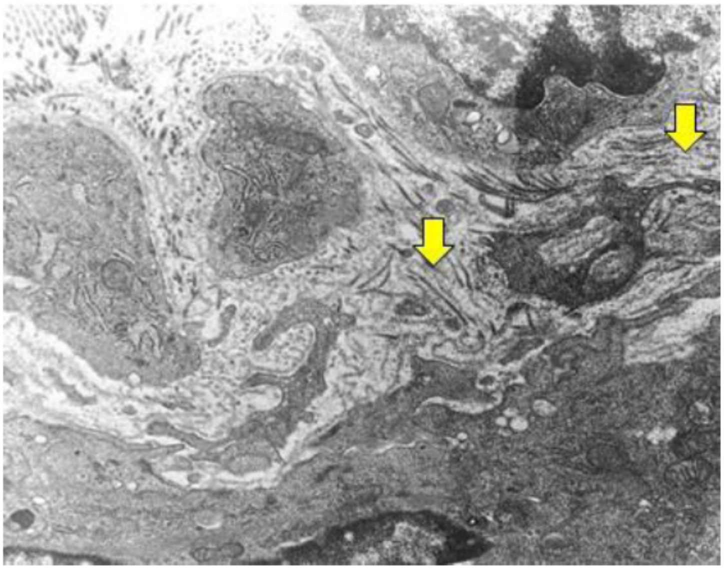
Figure 6. Electromicrographic that shows collagen fiber deposition in interstice at the early-stage of extracellular matrix remodeling. Electron microscopy, 7.000X. Source: Authors.



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3.2 Biomodulators electrotherapies and plasma jet application in the tissue repair context

Nowadays, it has been used some biomodulator therapies able to help in tissue repair process and act with redox effects such as laser photobiomodulation, LEDs and ozone therapy. They are able to generate an increase of ATP biosynthesis, inflammatory cells proliferation, fibroblasts and myofibroblasts, neo-angiogenesis and collagenesis (Sperandio et al., 2010; Medrado et al., 2008). Even a promising microbicidal effect has been associated to ozone and red laser with 660nm wavelength when they are directly applied to the injured area stained with a such photosensitizer chemical compound. It takes place due to the photosensitizer activation by the light which ends up in ROS generation and goes to pathogens' death. The photodynamic therapy has widely been used in dermatology and many studies has showed its potential for treating neoplasia (Issa & Manela-Azulay, 2010)

LED has been described as able to promote vasodilatation and generate rise at local microcirculation with greater oxygen supply and nutrients in tissue. Minatel et al. (2009) and Siqueira et al. (2009), reported that LED has been able to stimulate increase of collagen synthesis and accelerate cell metabolism, besides to contribute for reducing pain and increasing chances of obtaining a normotrophic scar. Such therapy has commonly been used since it does not emit radiation capable to injury the cornea. Moreover, it does not promote increase in site temperature, is portable, of easy application, unpainful and relatively low-cost (Minatel et al., 2009; Siqueira et al., 2009; Moura et al., 2014)

Also, other therapy that has also been used to support tissue repair process is the ozone therapy. Its way of action is straightly linked to the capability for exercising anti-microbial and immunomodulator activity in the tissue repair. Ozone is a natural compound of the atmosphere characterized for having one molecule composed by three atoms of oxygen and a strong oxidant action (Shulz, 1986). Ozone started to be used in the First World War, initially in Germany and Soviet Union, and posteriorly, that technique was spread throughout the Europe. Its influence over tissue repair has been documented (Anzolin & Bertol, 2018) and its therapeutic action is promoted by neutrophil activation which ones can inactivate many kinds of microorganisms through an oxidative outbreak (Borges, 2010). Another study has demonstrated ozone gas may favor the mechanism of protein synthesis by the host, increase on both amount and activity of ribosomes and mitochondria in the cells, as well as for oxygen in tissues (Rowen, 2018).

Recently, another kind of gas has been used as biomodulator therapy able to stimulate wound healing – plasma jet. In physics, the plasma is considered as the fourth matter stage because since it is a gas with high energy content (Chang & Chen, 2016). That term comes from the Greek and means "something molded". And it was described by the North American physic-chemistry Irving Langmuir in 1928 as a diverse combination of gas constituents with high level of ionization similar to the blood plasma. It is formed by ions, electrons, photons and neutrons, all of which are active species, capable of generating numerous reactions, which can be physical and/or chemical (Heinlin et al., 2010).

Plasma can be naturally found, in the environment or developed in a laboratory. In this case, the plasma is maintained through an external application of energy usually through an electromagnetic field. Thus, this technology has aroused even more interest in recent years, although Its use has already been described in literature since long time ago due to its utilization in sterilization process of several materials as medical equipment and food package (Kong et al., 2009).

In a study carried out in 2007 by Stolz et al., it was possible to evaluate the action of low temperature argon plasma in the treatment of different infectious diseases of the skin and chronic wounds, resulting in the reduction of pathogenic microorganisms at the site and, indirectly, favoring the tissue repair process. Additionally, the technique was well supported in almost all cases and had no side effects. Other studies have also shown that plasma at low temperatures is capable of accelerating the wound healing process mainly through a significant reduction in bacterial load making it a new alternative for skin and wound disinfection (Isbary et al., 2010; Stolz et al., 2007; Fridman et al., 2007).

The main sources of cold atmospheric plasma are the dielectric barrier discharges (DBD) and atmospheric pression plasm jet (APPJ). DBD is a direct source of plasma to the target to be treated and the device usually has a larger area to the plasm application. Regarding APPJ, plasma jet is an indirect source once that the electrode which generate the plasm is located in a device similar to a pen, that so, is ignited inside the device by using a gas that flows throughout the pipeline. For having a better control of discharge, the most of that plasma jet equipment handles noble gases (helium and argon) along with molecular gases (nitrogen and oxygen) (Bernhardt et al., 2019; Gan et al., 2018).

ROS and reactive nitrogen species (RNS) are generated from the characteristic gases of the atmospheric air. The ROS such as ozone, hydroxyl and superoxide, and the RNS, for instance, oxide nitric, are both considered as responsible for the plasma biologic effects interfering on biochemistry process as long as they interact with the target biomolecule and result in the formation of many chemical molecules that act as a secondary messengers (Von Woedtke et al., 2019; Stratmann et al., 2020).

Since plasma application is able to promote the increase of oxide nitric (ON) concentration in adjacent tissues, it may be attributed to this chemical mediator an important vasodilator effect at stimulating microcirculation increase. As well, it facilitates tissue oxygenation, and the arrival of nutrients and inflammatory chemical mediators being able to hasten up to 24.6% the time of healing process (Weltmann et al., 2009; Daeschlein et al., 2012).

A cohort study carried out in 2016 by Kisch et al., evaluated the action of cold atmospheric plasma (CAP) on skin microcirculation. The results showed that after the application of CAP there was a significant and immediate increase in saturation and local blood flow. These findings state data obtained in other studies that tested the effectiveness of CAP in the healing process. However, it is suggested that further research be carried out to verify whether this treatment would be able to improve microcirculation in diabetic foot ulcers, in order to stablish protocols for the application of a new adjuvant therapy to assist in the tissue repair process (Kisch et al., 2016).

Isbary et al., in 2012, proved that using plasma was able to significantly reduce the bacterial load in chronic wounds. In another study, published in 2013, the same authors suggested that the application of cold plasma was able to accelerate the healing process (Isbary et al., 2012). Then, in 2016, Chuangsuwanich et al., also performed a prospective randomized study that showed the efficacy of plasma jet treatment in patients with pressure ulcers (Chuangsuwanich et al., 2016).

Other findings in the literature indicate that cold plasma has also been shown to be effective in the treatment of patients with skin cancer. They show a significant decrease in local tumor growth as well as a reduction in tumor volume, without showing damage to adjacent tissues and cells. Another benefit from the application of plasma, in addition to the cytotoxic effect on cancer cells, would be related to the ability of this therapy to stimulate the immune system favoring tumor regression. Additionally, its use as adjunctive therapy in the treatment of psoriasis and atopic dermatitis has been reported (Gan et al., 2018).

The plasma jet, more precisely the argon one, competes with the traditional ablative laser technique. Since it is an electrosurgical procedure, the plasma jet has an action mediated by an interaction with the tissue and aims to promote tissue restructuring, with aesthetic purpose. Once it is a device widely used with the objective of stimulating skin regeneration with consequent reduction of wrinkles and expression lines, the plasma jet has become well known in the market. Due to that, plasma is directly used, which uses the skin (or other tissue) to couple the electrode in order to close the field and allow the passage of current (Fridman et al., 2008). A hot plasma jet is used, in which a direct current discharge is capable of generating perceptible heat in the skin tissue. In addition, it produces and transports a chemical element in the form of a gas, nitrogen (N) (Cerqueira et al., 2021).

By the application of the thermal plasma jet, energy in the form of heat is released through a discharge of direct current. Once offered, this energy will be transported to the target tissue, promoting thermal damage derived from the controlled induction of heat generated by the application of plasma. From this trauma in the tissue, some events are initiated with the purpose of promoting the repair of the injured tissue. Therefore, fibroblasts are stimulated to synthesize collagen favoring the restructuring and improvement of tissue quality (Heilin et al., 2010; Chang & Chen, 2016).

Additionally, recent studies have highlighted plasma jet as an efficient therapeutic resource to hair treatment, particularly in cases of *alopecia areata*. According to Cerqueira et al. (2021), besides its bactericidal and vasodilator effects, plasma jet was able to produce favorable results in cases of alopecia, and authors suggest that such effect may be resultant from the stimulus to the precursor collagen cells, the fibroblasts as well as from the cytokines biosynthesis and growth factors, as well as the already documented increase of hair follicles diameters (Babossalam et al., 2020).

4. Conclusion

By the complexity of tissue repair, biomodulator therapies have been developed as a good alternative to the healing process. Such approach may be justified for giving quicker solution to the tissue repair, consequently reducing time of treatment, cost of medical hospitalization and so, reducing negative impacts in life quality of the population. Although there is a growing number of studies that highlighted the biomodulator positive effects from the laser photobiomodulation utilization, LEDs and ozone therapy compared to plasma jet, it is an urgent need for new studies which scrutinize its potential for biomodulator action in different phase of healing process.

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