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CHRONIC WOUNDS IN DIABETICS: PERSPECTIVES AND TREATMENTS

FERIDAS CRÔNICAS EM DIABETES: PERSPECTIVAS E TRATAMENTOS

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Abstract

Objective and Methodology: We carried out a systematic review of the therapies used to improve the healing of diabetic wounds. Bibliometric approaches analyzed here showed a continuous and progressive increase in publications' quantitative and qualitative parameters. Results: Different technologies for managing and treating wounds were observed. For physical devices, negative pressure wound therapy stood out, showing as main effects moisture reduction, modulation of the inflammatory responses, and proliferation of granulocytes in the lesion. Bioengineered cell and tissue therapies have also been widely used for biological devices, which have demonstrated effectiveness in reducing inflammation, cell proliferation, stimulating collagen production, and developing granulation tissue. Conclusion: These therapies were able to act in wound healing, accelerating this process or considerably reducing the wound area, making them beneficial to diabetic patients.

Keywords: Diabetes. Impaired Wound Healing. Tissue Regeneration. Therapy.

Resumo

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Objetivo e Metodologia: Foi realizada uma revisão sistemática das terapias utilizadas para melhorar a cicatrização de feridas diabéticas. As abordagens bibliométricas aqui analisadas mostraram um aumento contínuo e progressivo dos parâmetros quantitativos e qualitativos das publicações. Resultados: Foram observadas diferentes tecnologias para manejo e tratamento de feridas. Para os dispositivos físicos, destacou-se a terapia de feridas por pressão negativa, mostrando como principais efeitos a redução da umidade, modulação das respostas inflamatórias e proliferação de granulócitos na lesão. As terapias de células e tecidos de bioengenharia também têm sido amplamente utilizadas para dispositivos biológicos, que demonstraram eficácia na redução da inflamação, proliferação celular, estimulação da produção de colágeno e desenvolvimento de tecido de granulação. Conclusão: Essas terapias foram capazes de atuar na cicatrização de feridas, acelerando esse processo ou reduzindo consideravelmente a área da ferida, tornando-as benéficas para pacientes diabéticos.

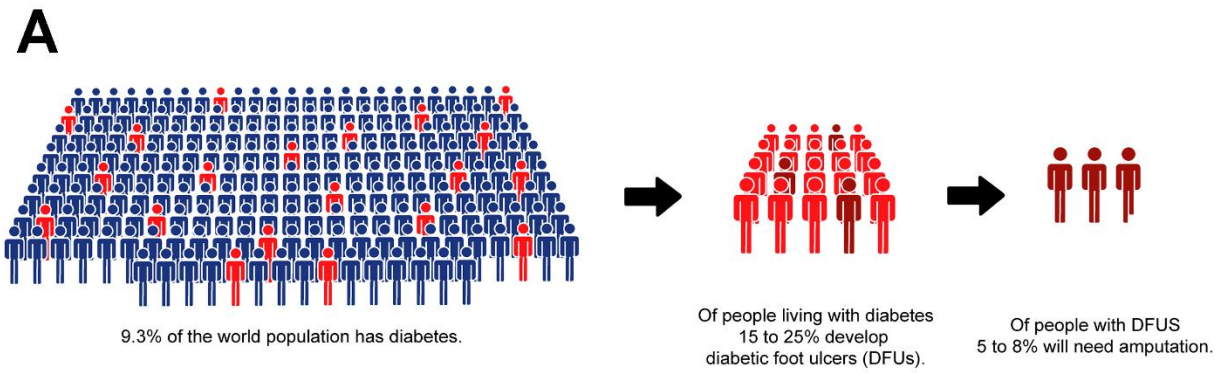
Palavras-chave: Diabetes. Cicatrização Prejudicada. Regeneração Tecidual. Terapia.

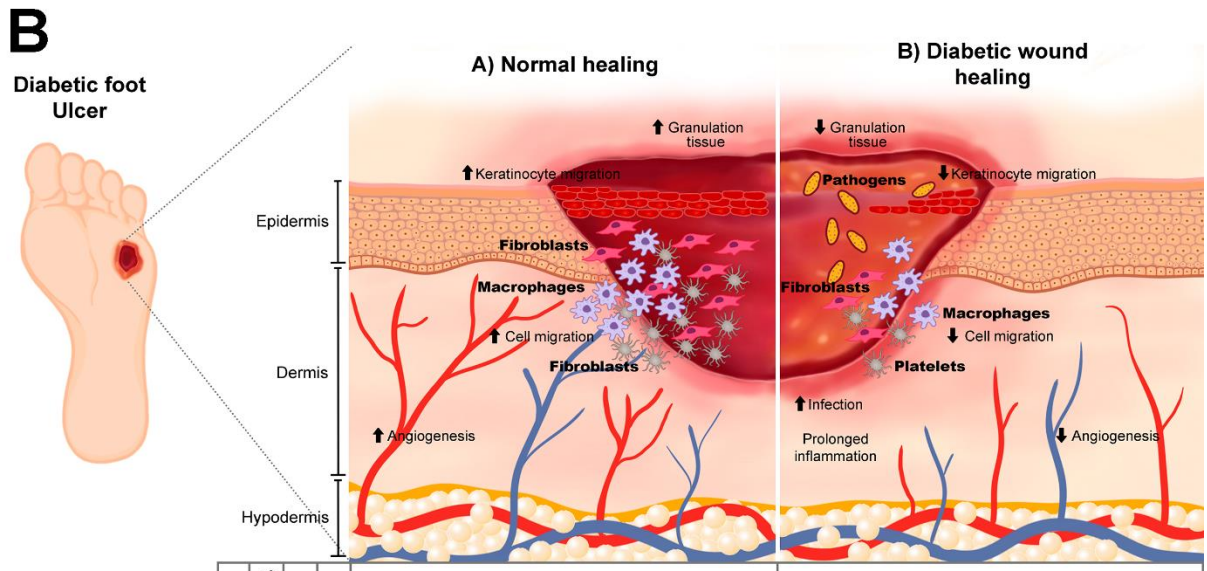
Introduction

Diabetes mellitus is a metabolic syndrome with multiple etiology. It is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Diabetes represents a critical public health challenge with a high incidence in the world's population (ZIMMET et al, 2016). In 2019, 463 million adults had diabetes (9.3% world population, Figure 1A). It is suggested that the number of cases will increase to 578 million (10.2%) in 2030 and to 700 million (10.9%) in 2045 (IDF, 2019). Regarding the treatment, changing inadequate dietary habits, losing weight, and regular exercise are considered first-choice therapies in treating metabolic syndrome (McLELLAN et al., 2007). However, in addition to lifestyle changes, interventions are also needed using different technologies in continuous care that does not always lead to a cure.

Among the most common and severe complications of diabetes mellitus is the impairment of self-repair and tissue healing abilities. At least 15% of all patients with diabetes will at some time have a non-healing wound despite insulin treatment and a meticulously controlled diet (CHITTEDEN: SKHAMI, 1991). The healing process is impaired in diabetes due to this disease's complex pathophysiology, which involves vascular, neuropathic, immunological, and biochemical problems (GREENHALGH, 2003). In normal healthy conditions, the wound healing process can be divided into four phases overlapping in time and space: hemostasis, inflammation, tissue formation, and tissue remodeling (Figure 1B) (MAJEWSKA; GENDASZEWKA-DARMACH, 2011). However, diabetic wounds do not

follow an orchestrated and healthy healing cascade (MUSTOE et al., 2006) and may turn into chronic wounds. Chronic wounds exhibit a pathologically delayed healing process (OLSSON et al., 2018).





Phases		Time		A) Normal healing	B) Diabetic wound healing
Hemostasis			Immediate	- Vasoconstriction - Platelet activation and aggregation - Coagulation - Hemostatic buffer	- Deficient vascular supply - Increased risk
Inflammation			2 - 9 days	- Inflammatory - Cell recruitment - Debridement - Elimination of microorganisms - Neutralization of pathogens	- Delayed recruitment of neutrophils - Neutrophils remain after 72 hours - Persistent inflammation - Hyperglycemia allows bacterial growth - Slow/ineffective activity of neutrophils and macrophages
Proliferation			9 - 20 days	- ECM Synthesis - Angiogenesis - Dermis and epithelium reconstruction	- Reduction in collagen deposition - Low fibroblast activity - High levels of MMPs - Low ECM production
Remodeling			≥ 21 days	- ECM reorganization - Collagen rearrangement - Scar formation	- Low tensile strength

Figure 1: (A) Frequency of diabetes and DFUs in worldwide population. (B) Comparative illustration of the four main stages of healing: normal and diabetic wounds. ECM: extracellular matrix; MMP: metalloproteinase. Adapted from Perez-Favila et al.

Molecular events are associated with failures in the wound healing process. High blood glucose increases blood vessel stiffness, which in turn causes slower circulation and microvascular dysfunction, resulting in reduced tissue oxygenation. In addition, vascular changes are also responsible for reducing the migration of leukocytes to injured tissue (GREENHALGH, 2003). The consequences of these problems are prolonged inflammation, decreased angiogenesis and neovascularization, dysfunction in fibroblasts and keratinocytes, damage caused by reactive oxygen species and the formation of advanced glycation end products, high expression of metalloproteases, decreased patient's immunological resistance and neuropathy (GUO; DIPIETRO, 2010). All these events impair wound healing, with one of the most common complications being diabetic foot ulcers (DFUs).

DFU is a severe and prevalent complication of diabetes and affects 15-25% of those living with the disease (Figure 1A) (GERAGHTY; LaPORTA, 2019). Of this total, in 40–80% of the cases, the infection reaches the bone, leading to osteomyelitis (GERAGHTY; LaPORTA, 2019). DFUs are characterized by excessive or prolonged inflammation, persistent infections, generation of drug-resistant microbial biofilms, and the failure of dermal and/or epidermal cells to respond to stimuli for tissue reparation (EDMONDS, 2012). It also has been associated with venous insufficiency, arterial disease, prolonged pressure, or neuropathy (RICHMOND et al., 2013). In consequence, these kinds of wounds cause pain and are associated with significant morbidity, including limited mobility, social isolation, depressed mood, and altered individual sleep patterns (SALOMÉ et al., 2011). All these limitations directly affect the DFUs, patients and disturb their daily activities (FRYKBERG; BANKS, 2015). In addition, DFUs are an important risk factor for lower-extremity amputation. It has been estimated that approximately 5% to 8% of DFU patients will require major amputation within one year, especially in patients with peripheral arterial occlusive disease (KIM et al., 2018). In terms of cost, the International Diabetes Federation estimated an annual expenditure of about $760 billion for diabetes care in 2019 worldwide, and from this total, 25–50% is related to DFUs (KANTOR, MARGOLIS, 2001). Regards to the mortality, the rates associated with development of a DFU are estimated to be 5% in the first 12 months, and 5-year mortality rates have been estimated at 42% (EVERETT; MATHIOUDAKIS, 2018).

Given this scenario, the development of new strategies which increase the therapeutic effectiveness of treating chronic wounds has become the focus of diabetes research. Currently, there are more than 3,000 types of products on the market to treat wounds that are difficult to heal, such as diabetic ulcers (JAFFE; WU, 2009). DFUs are heterogeneous, so no single dressing is ideal for all wound types. Among these options, the gold standard is the use of alginates, hydrogels, foams, and hydrocolloids, which help to maintain an environment with ideal humidity conditions (BROUSSARD; POWERS, 2013). More sophisticated technologies have also been used, but with limitations due to their high cost and questionable efficacy (JAFFE; WU, 2009). These modern therapies are based on different methodologies, such as the use of growth factors, skin grafts, stem cells, nanoparticles, oxygentherapy and negative pressure, among others. Here, we performed a scientometric evaluation and systematic review of the products and therapies that have been studied and indicated to improve the healing of diabetic wounds.

Material and Methods

A scientometric and systematic review was performed using the Web of Science database from 1991 to 2019. The survey was conducted in July 2020, and a total of 5.485 articles were found. The articles were selected using the following terms: “healing" AND "diabet*" AND "ulcer*" OR "healing" AND "diabet*" AND "chronic*" OR "healing" AND "diabetic foot" OR "wound" AND "diabet*" AND "ulcer*" OR "wound" AND "diabet*" AND "chronic*". We searched for papers that contained these words in the title, abstract, or list of keywords. Inclusion criteria were: (*i*) wound healing; (*ii*) diabetes; and (*iii*) treatments. On the other hand, grey literature and review articles were excluded. After reading the abstract, 3.967 articles were considered outside the scope of this systematic review, and 1.518 were included (Figure 2). Data extracted from eligible scientific articles included: scientometric data (year of publication; the number of citations; the name of the journal and its impact factor); study methodology (test adopted; type of treatment, technological devices, surgical techniques, compounds used to treat the chronic wounds).

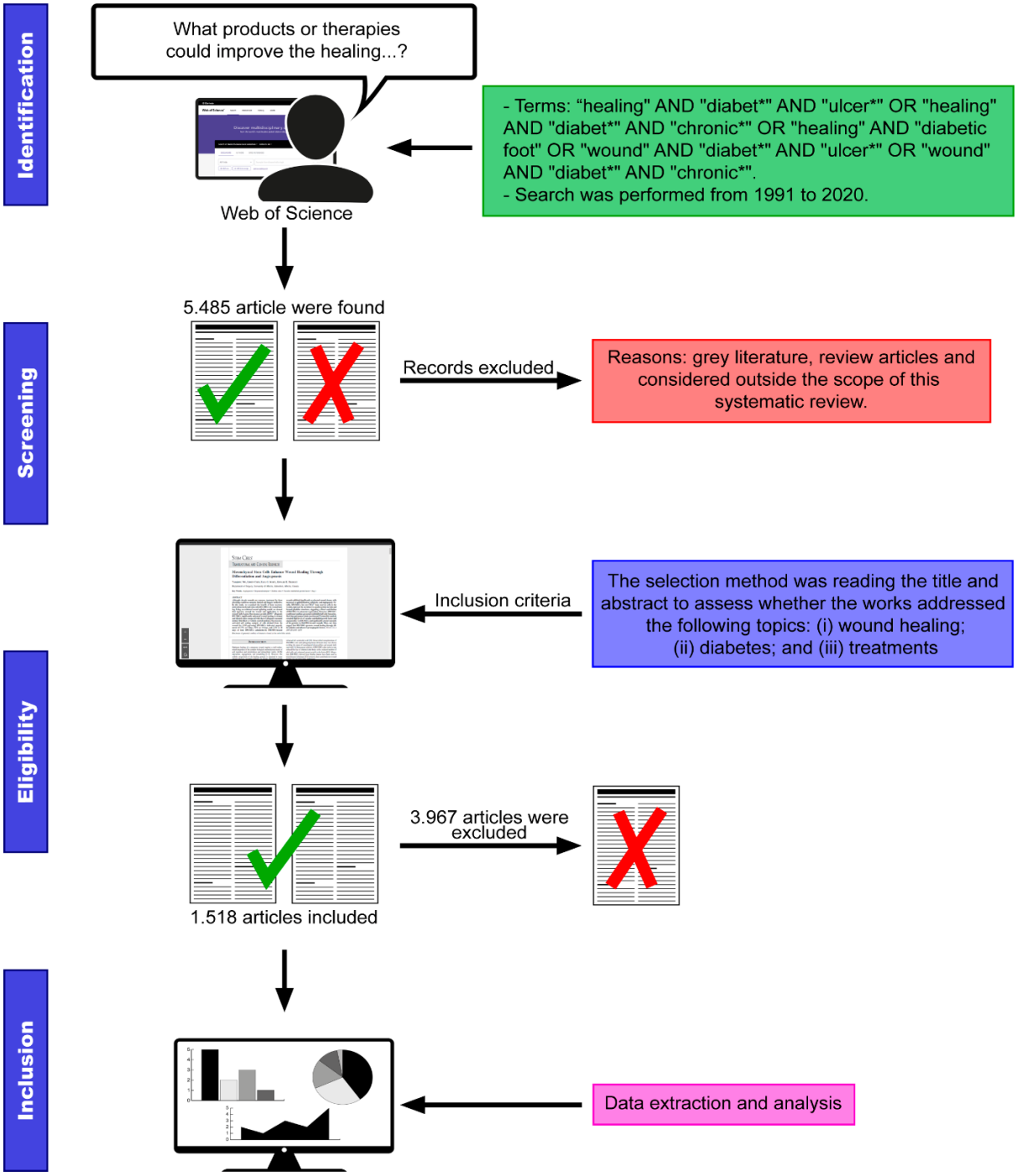


Figure 2: Systematic review methodology. 5.485 articles were found in the Web of Science database using the selected terms. After applying the inclusion and exclusion criteria, 1.518 were used in data analysis.

Statistical analysis

Over time, the increase in scientific production was evaluated by the proportion of articles published within the theme to the total number of articles present in the database. For this, the Spearman correlation test was used through the color.test function of the Stats package

at the 5% significance level (BEST; ROBERTS, 1975). The distribution of the articles concerning the techniques, equipment, drugs, and areas addressed was analyzed through the descriptive statistical analysis represented in graphs obtained via the ggplot2 package (WICKHAM, 2016). The effects of the treatments performed in the articles were evaluated by converting the data into a Bray-Curtis distance matrix through the Vegdist function. After the conversion, Principal Coordinate Analysis was achieved through the Cmdscale function in the Vegan and Stats packages, respectively (OKSANEN et al., 2013). Alluvial Plot was made to associated of each kind of equipment with the cells that proliferated in the treatment (LANGFELDER; HORVATH, 2012).

Results and Discussion

Trends and quality indicators of articles addressing wound healing in diabetics

Temporal publication trends regarding diabetes wound healing treatments are constantly and significantly increasing ($r = 0.94$, $p < 0.001$) over the years (Figure 3A). This improvement in scientific production may reflect the continuous increase in the number of cases of diabetes across the world, which generates the most significant investment by governments and private companies searching for new medicines. Currently, 463 million adults suffers from diabetes (IDF, 2019), and every 30 seconds, a person is lost to diabetes.

The number of citations and the impact factors (IFs) of journals often indicate research quality. We observed that the number of citations ranged from 0 to 873 (Figure 3B). Typical behavior of bibliometric research could be observed here; the older papers tend to have more citations (YU; LI, 2007). In a general context, the journals analyzed in this study had IFs ranging from 0.03 to 59.1, with a mean value of 3.31 (Figure 3C). This high mean IF value indicates that, in general, articles on potential treatments for wounds in diabetes are published in journals of high-quality scientific communication and recognized in the scientific world.

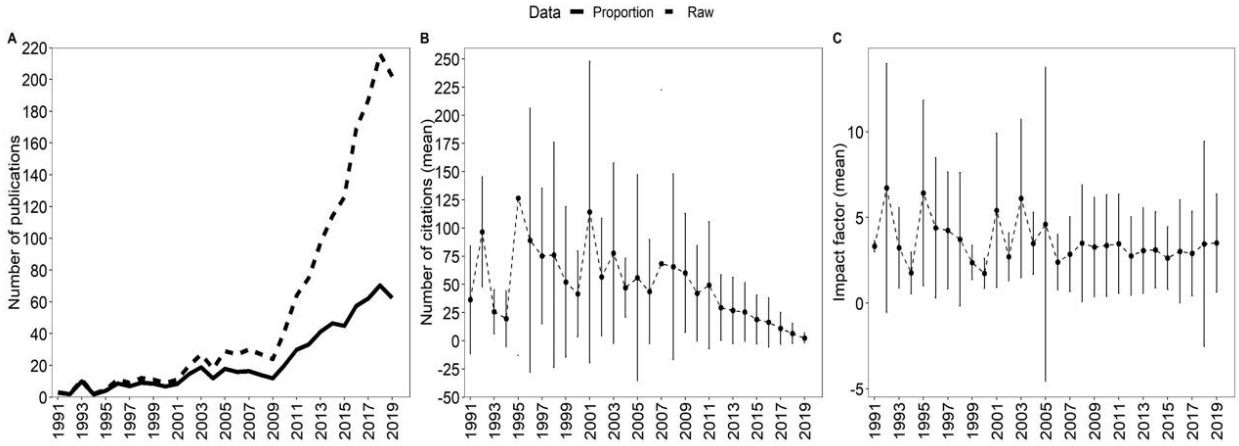


Figure 3: Bibliometric information about chronic wounds treatment in diabetes. (A) the absolute number of publications per year (continuous line), and the proportion of publications to the total of publications per year on the platform (dotted line). (B) frequency of citations per article. (C) journal's impact factor.

Survey methods in wound healing of diabetics

Before selecting a wound healing model, many different factors must be considered because the wounds are heterogeneous, and many factors influence the wound healing process. Here we list the models most used in articles regarding chronic wounds in diabetes. Most of the studies (56.6%) evaluated the healing process directly in diabetic patients, and the research was conducted with the authorization of the patients and the ethics committee in human research (Figure 4A). In those studies, most patients had their feet affected. Effects on feet in these patients are associated with a chronic process that includes complications from neuropathy, vasculopathy, immunodeficiency, and uncontrolled blood glucose, which create favorable conditions for the onset of plantar foot ulcers. The common procedures for DFUs treatment today include local wound care with surgical debridement and control of active infection, dressings that promote a moist wound environment, vascular assessment and glycemic control (EVERETT; MATHIOUDAKIS, 2018). Even with treatment, many cases of diabetic foot deterioration and limb amputation are necessary.

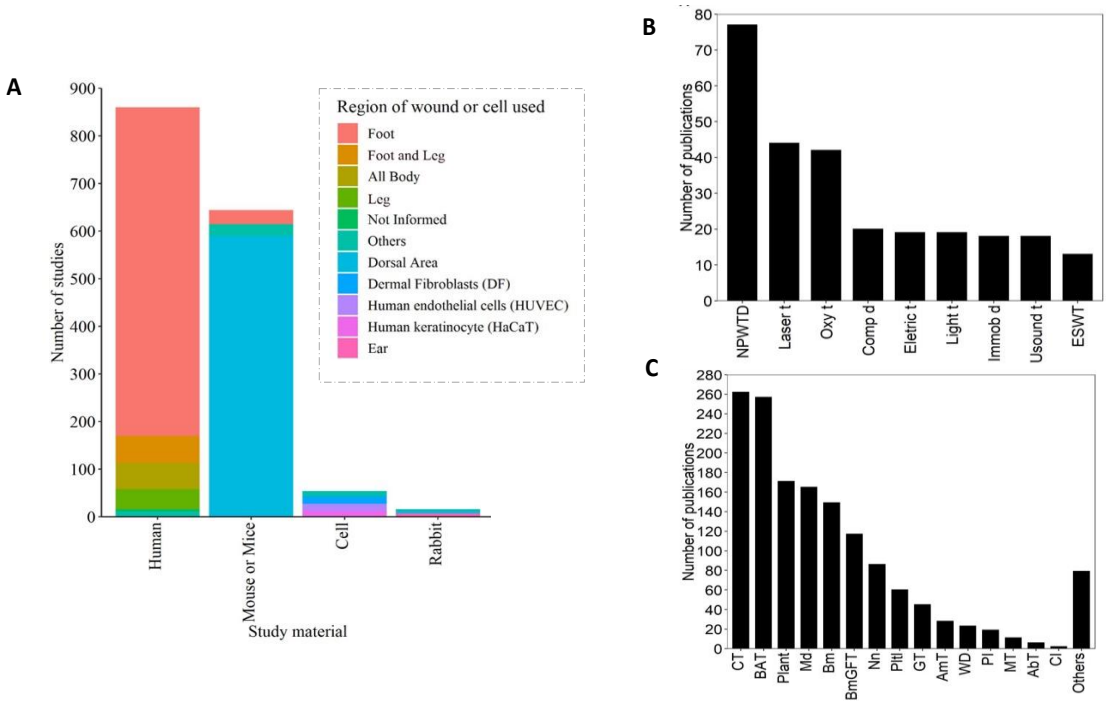


Figure 4: (A) Analysis of the experimental model used in diabetic wound healing studies. Main treatments used to heal diabetic wounds. (B) Number of articles that used physical methods (Group I). (C) Number of articles that used biological materials (Group II). **NPWTD:** Negative pressure wound therapy; **Laser t:** Laser therapy; **Oxygen t:** Oxygen therapy; **Comp d**: Compression devices; **Electric t:** Electric therapy; **Light t**: Light therapy; **Immob d**: Immobilization devices; **Usound t:** Ultrasound therapy; **ESWT**: Extracorporeal shock wave therapy; **CT**: Cell therapy; **BAT**: Bioengineered alternative tissues; **Plant**: plant; **Md:** Medications, **Bm:** Biomolecules; **BmGFT:** Biomolecules and Growth factor therapy; **Nn**: Nanoparticles; **GT:** Gene therapy; **AmT**: Antimicrobial therapies, **WD:** Wound dressings; **PI**: Protease inhibitors; **MT:** Maggot therapy; **AbT:** Antibody therapy, **CI:** Connexin inhibitor.

Regarding experimental models, rodents were the most used animals for diabetes studies. Usually, the choice for this model is associated with its relatively low cost, small animal size, short generation interval, and high availability. In total, 644 articles were identified, with predominance in models using dorsal wounds. Among the methodologies used, we can highlight: 1.) genetic models, in which animals have a gene mutation or a knock-out of one or more genes were produced; 2.) chemically induced models, in which diabetes is induced by drugs; 3.) biochemically induced models, in which animals are submitted to diets rich in sugars and fats; and 4.) models of spontaneous diabetes, such as Biobreeding mice and Non-Obese Diabetic mice. Many of these methodologies share similar characteristics to diabetes and allow experimentation that would be impossible in humans (SRINIVASAN; RAMARAO, 2007). In addition, non-rodent animals and cell cultures have rarely been used as an experimental model

in diabetes chronic wounds. The low use of *in vitro* systems can be explained by the limitation of this technique for the study of multifactorial metabolic diseases.

Diabetic wound treatments

We created two groups to describe the main treatments used to cure diabetic wounds. Group I includes the physical methods, and Group II consists of the treatments performed with biological material, drugs, nanomaterials, or an isolated chemical compound. Among the physical methods, the devices using the techniques of negative pressure wound therapy (NPWTD), laser therapy (Laser t), and oxygen therapy (Oxy t) stand out (Figure 4B). NPWT or vacuum dressing (VAC) is a non-invasive method that consists of an open-cell foam dressing covered with an adhesive drape. The dressing is connected to a vacuum pump which creates and maintains a continuous or intermittent sub-atmospheric pressure, depending on the type of wound being treated and the clinical objectives (GREGOR, 2008). The continued vacuum draws out fluid from the wound and increases blood flow, decreases edema, stimulates the early development of granulation tissue, and causes wound, bacterial load, and proteases concentration reduction at the injury (JAFFE; WU, 2019). Reduced numbers of diabetic foot amputations were demonstrated in groups of patients treated with NPWT compared to those treated with traditional therapies (FRYKBERG; WILLIAMS, 2007). All these positive effects contribute to successful treatment and faster healing, decreasing medical resources and nursing-care expenses (LAVERY et al., 2007). The decision to use this type of treatment should consider the high cost of NPWT.

Among the laser therapy options, the low-intensity laser therapy (LLLT) is an alternative treatment capable of stimulating cellular metabolism through photobiomodulation. The physical and biological changes caused by laser in the tissue generate a low flow of free radicals in the wound, stimulate gene expression, fibroblast proliferation, collagen synthesis, and angiogenesis, and increase the production of extracellular matrix components, resulting in early epithelialization of the wound.[30] In addition, laser therapy has antibacterial activity (MONAMI et al., 2017). The biological effects of the laser depend on energy density, wavelength, dose quantity, and type of laser applied (SAMANEH et al., 2015). No adverse effects have been reported up to now. The third most used therapy in treating diabetic wounds was oxygen-based. Oxygen is a crucial component of the healing process because it modulates cellular responses and angiogenic activity (BISHOP, 2008). The oxygen supply in chronic wounds can improve and accelerate wound healing (DISSEMOND et al., 2015). Among the

therapies with oxygen, topical oxygen therapy stands out because it is a cheap, flexible method that does not have significant side effects. This treatment delivers oxygen to the wound through portable devices, which creates an external pressure and increases the oxygen concentration within the injured area (DISSEMOND et al., 2015). Alternatively, there is HBOT, a high-cost procedure that demands high efforts to be a prolonged daily treatment. In this method, the patient is placed in a chamber with high oxygen pressure, which results in the entry of large amounts of oxygen into the injured tissues (TIBBLES; EDELSBERG, 1996). According to the literature, patients who had diabetic foot ulcers and were treated with HBOT showed increased angiogenesis in the wound bed, improved collagen deposition and leukocyte function, and decreased edema (LONDAHL, 2013). This treatment has shown higher rates of fully healed DFUs and lower amputation rates (SHARMA et al., 2021).

Among the three methodologies cited, our results showed that the procedures performed with NPWT were the most used for wound healing in diabetes, being employed almost twice as frequently as laser and oxygen-based devices and four times more than other devices. Although physical methods are widely used, the data from the present study showed that studies about treatments in group II are more frequent than those in group I. In group II, the therapies performed with cells, bioengineered tissues, plants and their extracts, commercial drugs, and isolated biomolecules are widely used. Cell therapies and tissue bioengineering were the most cited (30% of publications).

Cell therapies are usually performed with fibroblasts, keratinocytes, bone marrow stem cells (BMSCs), platelets, and the vascular stroma cell fraction of adipose tissue (SVF). Those treatments induce cytokine expression, growth factors, and enzymes, stimulating wound regeneration (LIU et al., 2009). Regarding the mechanism of action of each cell type, keratinocytes act mainly in the release of growth factors, such as TGF-α, PDGF, bFGF, VEGF, TGF-β, and cytokines. However, they are not capable of synthesizing extracellular matrix. Fibroblasts, on the other hand, in addition to controlling cell proliferation, induce angiogenesis, modulate the inflammatory process, and produce an extracellular matrix rich in collagen and other proteins (YOU; HAN, 2014). BMSCs are multipotent stem cells capable of differentiating into chondrocytes, osteoblasts, adipocytes, myocytes, fibroblasts, epithelial cells, endothelial, and neuronal cells [39]. They release different chemical mediators that stimulate cells' proliferation, migration, and differentiation, participating in wound regeneration (CHEN et al., 2012). Preclinical studies with BMSCs showed its regenerative potential in chronic wounds, reducing the size of the ulcer, the scar, and the patient's pain (NOURIAN et al., 2019). Another

cell therapy used in the treatment of wounds is the use of platelets. Platelets regulate wound inflammation, have antibacterial activity, and increase the differentiation of immune cells (EISINGER et al., 2018). Furthermore, growth factors released by platelets stimulate cell migration, proliferation, differentiation, and angiogenesis (COBOS et al., 2015). Platelet mediators also stimulate the formation of extracellular matrix and the restructuring of connective tissue, contributing to tissue remodeling, an important step in wound healing (EISINGER et al., 2018). In addition, human SVF has been considered an attractive source of stem cells for the treatment of wound healing. SVFs are formed by a heterogeneous mixture of endothelial cells, fibroblasts, pericytes, preadipocytes, adipose tissue-derived stem cells (ADSCs), mast cells, and smooth muscle cells (GENTILE et al., 2012). They accelerate the healing process by promoting fibroblast migration, stimulation of angiogenesis, and the production of collagen and extracellular matrix in the injured tissue (BI et al., 2019).

Bioengineered Alternative Tissues (BATs), used as skin substitutes, are represented by a heterogeneous group of sophisticated biomaterials formed by acellular and cellular components, whose main objective is to stimulate the host to regenerate the injured tissue, resulting in a new functional skin (SNYDER et al., 2020). Previously, acellular BATs were basically composed by metal and plastic joint prostheses which meant to fill a space and function mechanically without cells. Recently, with the innovations in this area, synthetic acellular materials, such as porous foams and fibrous scaffolds included the delivery of growth factors to stimulate cellular behavior and matrix production, collagen delivery vehicles containing bone morphogenetic proteins to enhance bone tissue repair (GLASSMAN et al., 2008). Cellular BATs, on the other hand, contain live cells, which are usually skin cells and are arranged in a matrix-forming a single layer or bilayer.

Correlation between biological effect on the wound and treatments

To better understand the effect of each treatment using physical devices on wound physiology, a Principal Coordinate Analysis test was performed, which retained 90.78% of the information in two axes (Figure 5A). As a result, it can be highlighted that NPWTD devices promoted the reduction of moisture and wound inflammation (Figure 5B). These same effects were also associated with laser therapy (Laser t), which also had an antibacterial effect (Figure 5B). Regarding the inflammation, it plays an important role in initial phase wound healing because it recruits leukocytes to the wound area and contributes to the release of enzymes and

reactive oxygen species (MASSON-MEYERS et al., 2020). However, the inflammation needs to happen fast and only initially phase, whereas it needs to be prevented in posterior stages. At that moment, NPWTD and laser therapy are interesting for reduce wound inflammation (GONZALES et al., 2016). On the other hand, prolonging the inflammation process can happens because of the presence of microorganisms and their toxins in the wound. This prolongation may cause the wound to enter the chronic state, and therefore, it cannot be healed. Wound infection is a known predictor of poor wound healing and amputation (ACAR et al., 2017). Since laser therapy could has antibacterial activity, it can help heling process (Figure 5B).

Other common event during the wound healing process is an overproduction of reactive oxygen species in wound bed that may decrease the rate of wound healing (ACAR et al., 2017). Therapies such as the oxygen therapy (Oxy t) which present antioxidant and hypoglycemic effects and could reduce the production of reactive oxygen and assist the healing process (Figure 5B). NPWTD, Laser t and Oxy t caused a proliferation of granulocytes in the wound bed that provide protection against microbes.

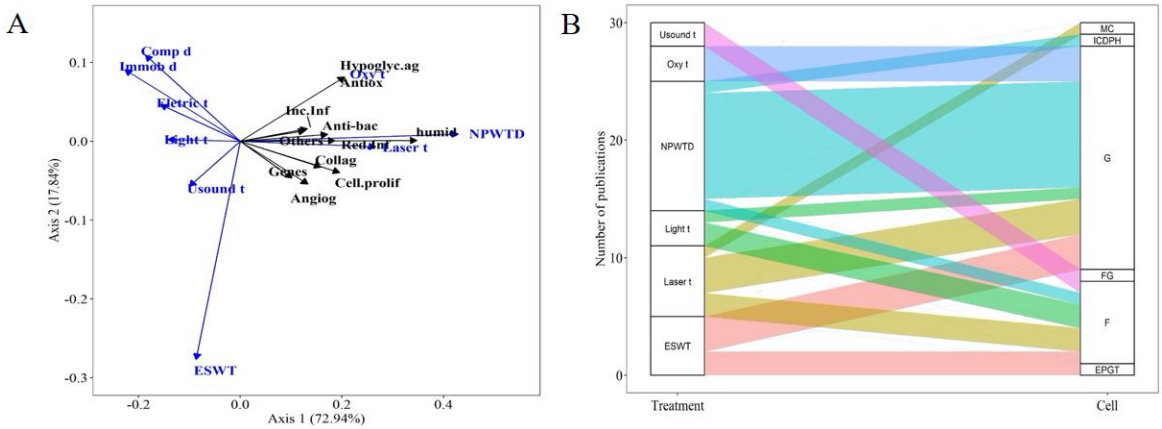


Figure 5: Correlation between biological effect on the wound and physical methods. **(**A) Principal Coordinate Analysis representing the relationship of physical devices (in blue) used to treat wounds in diabetics and their effects (in black). (B) Alluvial plot demonstrating the proportion of the relationship between treatments with different devices and the types of cells they promoted growth. **Comp d:** Compression devices; **Electric t**: Electric therapy; **ESWT:** Extracorporeal shock wave therapy; **Immob d**: Immobilization devices; **Laser t:** Laser therapy; **Light t**: Light therapy; **NPWTD**: Negative pressure wound therapy devices; **Oxy t:** Oxygen therapy; **Ultrasound t:** Ultrasound therapy; **MC:** Mast cells; **CDPHI**: Inflammatory cells and dinuclear and polynuclear histiocytes; **G:** Granulocytes; **FG**: Fibroblasts and granulocytes; **F:** Fibroblasts; **EPGT**: Epidermal proliferation and granulation tissue; **Antiox**: Antioxidant; **Anti-bac:** Anti-bacterial; **Humid:** humidity; **Hypoglyc ag**: Hypoglycemic agent; **Genes**: Genes; **Inc Inf**: Increased inflammation; **Red Inf:** Inflammation reduction; **Angiog:** Angiogenesis; **Cell prolif**: Cell proliferation; and **Collag:** Collagen.

We correlated the effects of treatments with wound physiology and found 4 profiles. In profile 1, the main effects were the reduction of inflammation, epidermal proliferation, increase in granulation tissue, and acceleration of wound closure (Figure 6). The treatments associated with this profile were tissue bioengineering, nanoparticles, and plant extracts. In profile 2, the effects observed were inflammation reduction, collagen deposition increase, and wound closure acceleration. The treatments associated with this profile were therapies with growth factors, nanoparticles, cell therapies, and the use of biomolecules or drugs. Profile 3 showed effects such as antibacterial activity, regulation of angiogenesis, collagen deposition, smooth muscle cell proliferation, stromal cells migration from adipose tissue, and increased wound healing speed. Treatments associated with this profile were larval therapies, protease inhibitors, antimicrobial therapies, and dressings. Finally, profile 4 was characterized by antioxidant, antibacterial, and hypoglycemic activities, stimulating angiogenesis, collagen deposition, smooth muscle cell proliferation, and healing acceleration. The treatments associated with this profile were mainly the use of platelets and plant extracts.

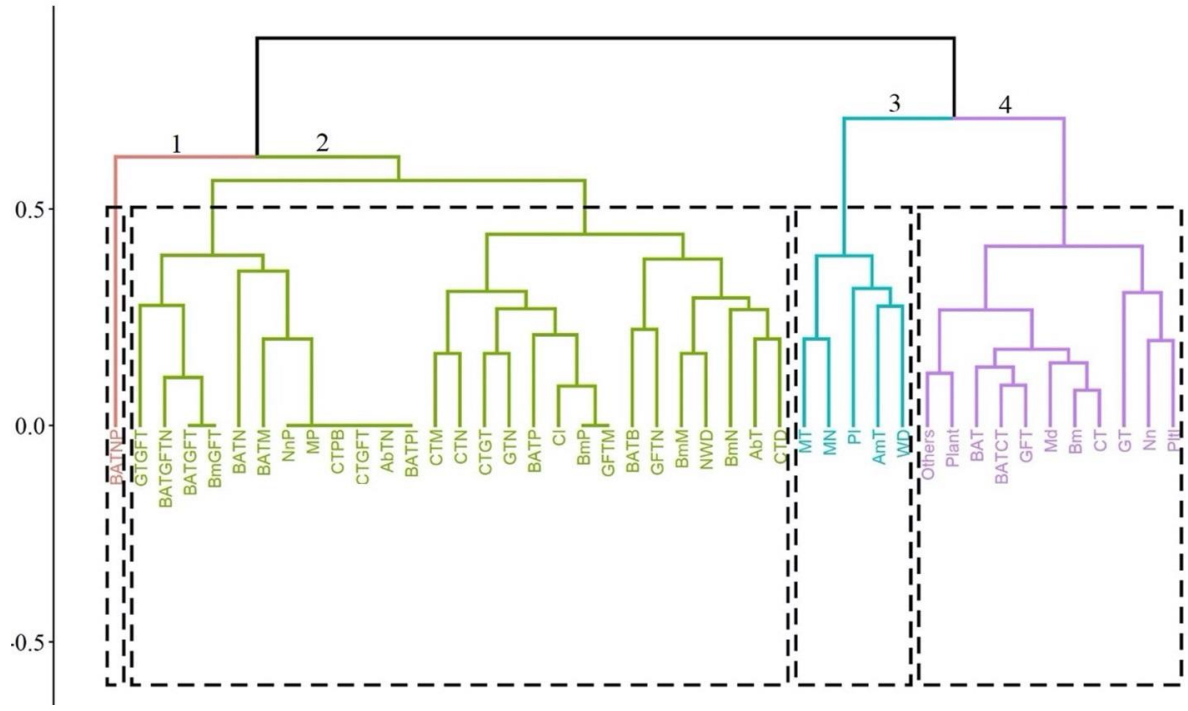


Figure 6: Dendrogram performed to group treatments according to their effect. The effects were divided into four profiles (1, 2, 3, and 4). **AbT**: Antibody therapy; **AbTN**: Antibody therapy and Nanoparticles; **AmT**: Antimicrobial therapies; **BAT**: Bioengineered alternative tissues; **BATB**: Bioengineered alternative tissues and Biomolecules; **BATCT:** Bioengineered alternative tissues and Cell therapy; **BATGFT**: Bioengineered alternative tissues and Growth factor therapy; **BATM:** Bioengineered alternative tissues and Medications; **BATN:** Bioengineered alternative tissues and Nanoparticles; **BATP**: Bioengineered alternative tissues and Platelets; **BATPI**: Bioengineered alternative tissues and Protease inhibitors; **BATGFTN**:

Bioengineered alternative tissues Growth factor therapy and Nanoparticles; **BATNP:** Bioengineered alternative tissues; Nanoparticles and Plant; **Bm:** Biomolecules; **BmGFT:** Biomolecules and Growth factor therapy; **BmM:** Biomolecules and Medications; **BmN:** Biomolecules and Nanoparticles; **BmP**: Biomolecules and Plant; **CT:** Cell therapy**; CTGT**: Cell therapy and Gene therapy; **CTGFT:** Cell therapy and Growth factor therapy; **CTM:** Cell therapy and Medications; **CTN:** Cell therapy and Nanoparticles; **CTD:** Cell therapy and Platelets; **CTPB:** Cell therapy; **CI:** Connexin inhibitor; **GT**: Gene therapy; **GTGFT:** Gene therapy and Growth factor therapy; **GTN**: Gene therapy and Nanoparticles; **GFT:** Growth factor therapy; **GFTM:** Growth factor therapy and Medications; **GFTN:** Growth factor therapy and Nanoparticles; **MT:** Maggot therapy; **Md:** Medications; **MN:** Medications and Nanoparticles; **MP:** Medications and Plant; **Nn**: Nanoparticles: **NnP** Nanoparticles and Plant; **NWD:** Nanoparticles and Wound dressings; **Pltl:** Platelets; **PI**: Protease inhibitors, and **WD:** Wound dressings.

Conclusions

The development of alternative and complementary therapies for the treatment of diabetic wounds has increased in the last 30 years. All bibliometric approaches analyzed here showed a continuous and progressive increase in publications' quantitative and qualitative parameters on this topic. Furthermore, it was observed that in recent decades there had been great interest in developing devices capable of promoting the healing of difficult-to-heal wounds, in which more conventional therapies are failing. Most of the therapies evaluated in this study were carried out in case studies. The most significant number of events was related to diabetic feet, a disease that usually causes limb amputation and has high morbidity and mortality rates. A wide variety of technologies for the management and treatment of wounds were observed in this study.

For physical devices, NPWT stood out, which the main effects were moisture reduction, modulation of the inflammatory response, and proliferation of granulocytes in the lesion. Bioengineered cell and tissue therapies have also been widely used, which have shown effects in reducing inflammation, cell proliferation, stimulating collagen production, and developing granulation tissue. Both physics and biological therapies were able to act in all phases of wound healing, accelerating this process or considerably reducing the wound area. That therapies have limited availability and are employed only when traditional treatments have failed. There are no drugs or devices available on the market that promotes the complete healing of chronic diabetic wounds, which signals the urgency of integrated therapies and the development of new therapeutic alternatives.

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