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Prevention and Control of Vascular Lesions in Diabetics and Coverages

Marineide Pereira de Brito [a], Hermita Érika de Sousa [b], Maisa de Medeiros Rocha [c], Andressa Brito Lira [d*]

[a] *Universidade Estácio de Sá, João Pessoa,58037-000 Paraíba, Brasil.*
[b] *Centro Universitário Mauricio de Nassau, Campina Grande, 58410-050, Paraíba, Brasil.*
[c] *Universidade Federal de Ouro Preto, Ouro Preto, 35400- 000, Minas Gerais, Brasil.*
[d] *Programa de pós-graduação em Produtos Naturais e Sintéticos Bioativos, Universidade Federal da Paraíba, João Pessoa,58051-900, Paraíba, Brasil. ∗ andressabritolira@hotmail.com*

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Abstract
Diabetes mellitus is a highly prevalent syndrome worldwide, which, unchecked, affects several organs and systems. This review aimed to present injury prevention and control strategies, as well as coverage already available on the market, coverage with propolis and new treatment perspectives. It is important to highlight some preventive measures to control injuries in order to avoid chronicity as well as a wide variety of coverings. The study of ecological and accessible coverings that uses propolis is growing, which has several biological properties. Therefore, it is necessary to develop new coverings taking into account the cost / benefit ratio.

Keywords: Diabetes mellitus; vascular injury; covers.

Prevenção e controlo das lesões vasculares nos diabéticos e coberturas

Resumo
O diabetes mellitus é uma síndrome de alta prevalência mundial, que, sem controle, afeta diversos órgãos e sistemas. Esta revisão teve como objetivo apresentar estratégias de prevenção e controle de lesões, bem como coberturas já disponíveis no mercado, coberturas com própolis e novas perspectivas de tratamento. É importante destacar algumas medidas preventivas para o controlo das lesões, de forma a evitar a cronicidade, bem como uma grande variedade de coberturas. É crescente o estudo de coberturas ecológicas e acessíveis que utilizam a própolis, que possui diversas propriedades biológicas. Portanto, é necessário desenvolver novas coberturas levando em consideração a relação custo/benefício.

Palavras-chave: Diabetes mellitus; lesão vascular; coberturas.

Introduction

Diabetes mellitus (DM) is conceptualized as a set of metabolic diseases, bringing together defects related to the action of insulin and/or production; or a defect of action and production simultaneous, leading to hyperglycemia. Hyperglycemia compromises nitrite oxide-mediated vasodilation, increasing the formation of glycation end products and pro-inflammatory factors (Dryden et al., 2017). Micro and macrovascular complications directly associated with diabetes mellitus are responsible for the dysfunction and failure of several organs; especially kidneys, eyes, heart, blood vessels and immune system; and the high mortality rate (Almeida et al., 2017, Verhulst, Loos, Gerdes &Teeuw,2019).

Diabetes mellitus has shown a high worldwide prevalence affecting 463 million of individuals, with the majority (79%) in developing countries. Projections for the year 2045 are worrying; these numbers will increase to 700 million living with this syndrome (Huang et al., 2020, IDF, 2019). The United States of America (USA) has over 30 million adults with diabetes mellitus, in addition to the estimate of around 84.1 million adults with pre-diabetes parameters, demonstrating the potential growth of diabetes in this population if no lifestyle interventions are implemented (Nhim et al., 2019). The number of individuals in the USA with chronic injuries is around 6.5 million (Garrand, Hozzein & Badr, 2017) and the Health System spends more than $ 25 billion a year on treating complications from wounds. In addition, the United Kingdom (UK) confirms the high-cost that Health Service pays for the management of chronic injuries per year, with amounts in 2005 that were equivalent to US$ 3.4 - 4.6 billion paid for services to diabetic patients with chronic injuries (Jarbrink et al., 2016, Xiao et al., 2016).

A Diabetic foot ulcer is one of the main complications of diabetes mellitus in the lower limbs, caused by peripheral

vascular disease, diabetic neuropathic disease or infection of the lesion. Among the patients with lesions in the lower limbs, 35% are diabetic foot ulcers and these are responsible for 80% of non-traumatic amputations (Ravazzani et al., 2016, Huang et al., 2020). It is estimated that 15% to 25% of people with diabetes mellitus will develop at least one diabetic lesion during their lifetime (Mariam et al., 2017). Hence they represent a serious and repetitive complication, in some extreme cases leading to amputation (Wang et al., 2019).

Taking into account the high rate of complications in the lower limbs of patients with diabetes mellitus, due to the lack of control and prevention of the syndrome and its consequences, this article presents information regarding the prevention and use of coverage available for treating acute and/or complex lesions in order to avoid their chronicity; including preventing limb amputation. New therapies were also reviewed, already in the implementation phase in health services and others that still need complementary studies to ensure their applicability.

Prevention and control of vascular injuries in diabetics

Metabolic control significantly reduces the negative evolution of chronic diabetes complications, including acute and chronic injuries of the lower limbs (IDF, 2019, Sociedade Brasileira de Diabetes, 2020). The diabetes educator must be part of the multidisciplinary team that must guarantee an integrated (Tan et al., 2020) and continuous metabolic control, the quality of the evaluation, the establishment of intervention goals and practices - glycemic monitoring, normalization of the lipid profile, body weight control and abolition smoking (IDF, 2019, Sociedade Brasileira de Diabetes, 2020).

Among the factors that interfere in the appearance of complex diabetic wounds, some can be modified directly by the patient, others cannot. Hyperglycemia, lack of hygienic care, lack of regular surveillance of skin integrity, early detection of lesions and relief of prolonged pressure in specific regions, are factors that can be modified by the patient and, if properly controlled, prevent injuries and their chronic evolution (Pereira et al., 2017).

Lifestyle management somewhat mitigates the strength of genetic predisposition as a risk factor for diabetes mellitus (Zheng, Ley & Hu, 2016). Studies have shown that severe lifestyle changes associated with pharmacological treatments prevent type 2 diabetes or delay the onset of this syndrome in patients at risk or with glucose intolerance. It is important to note that prevention, changes in lifestyle and diet, must extend to those individuals who present themselves within the parameters of pre-diabetes (Faludi et al., 2017; Pereira et al., 2017, Nhim et al., 2019). Control over the initial development factors is important in preventing diabetes mellitus in the infant and adult phases, which are the delay in introducing cow's milk to the newborn and the intrauterine exposure of maternal hyperglycemia (Zheng, Ley & Hu, 2016).

Tuberculosis and leprosy patients should be screened to diagnose diabetes early. Tuberculosis can stimulate glucose intolerance and, in patients with diabetes mellitus, make glycemic control difficult. Leprosy patients have a higher incidence in relation to tuberculosis, however the nature of this association is not well evidenced (American Diabetes Association, 2017).

Diabetic patients presented more bacteria from the wound surface to deep tissues, when compared to non-diabetic patients with wounds. Therefore, it is necessary to prevent and control the factors that help the proliferation of bacteria in the wound bed, as well as promote vascular repair that directly affects the neovascularization of the affected area (Wang et al., 2019). It is important to note that chronic wounds in the elderly are affected by physiological changes and alterations in the tissue repair process in response to aging. Therefore, it is necessary to monitor aged people before the appearance of injuries in individuals with chronic noncommunicable diseases (Makrantonaki, Wlaschek & Scharffetter-Kochanek,2017).

Finally, prevention programs must be implemented to reduce the incidence of diabetes and/or its complications. The awareness of individuals about the risk of developing the disease, a high risk profile compatible with pre-diabetes, helps the individual to not underestimate the risk that they face. The increase in the perceived risk of a disease is a prerequisite for preventive action. Communication between health professionals and patients must be effective and appropriate to the educational level of the assisted patient (Heidemann et al., 2019).

Commercialized coverages

The choice of the appropriate coverage for each injury must be guided by an understanding of the properties of the coverage and its ability to match the drainage level and depth of the injury (Ahmed, Getti & Boateng,2018, Shoham, Krieger & Tamir,2018; Ttable 1). An analysis regarding the presence or absence of necrosis and infection in the lesion is essential (Shoham, Krieger & Tamir,2018). The healing process is not stagnant, so the type of dressing can change during this process, depending on the amount of exudate and the depth of the lesion (Jeon & Kim,2018).

Moisture retention wound dressings include films, hydrogels, hydrocolloids, foams, alginates, and hydrofibers which are used in a variety of clinical situations (Silva et al., 2018). Hydrocolloids and hydrogels are impervious to air and water, and are long-lasting, but should not be used on exudative wounds because of their impermeable nature (Han & Ceilley, 2017). The coverings of Hydrogel, Hydrocolloids and foams promote autolytic debridement, maintenance of an adequate environment for re-epithelialization, absorption of exudate and prevention of additional trauma (Gianino, Miller & Gilmare, 2018, Silva et al., 2018). The foam protects the wound and prevents dehydration, keeping the environment moist (Jones & Foster,2018). Despite the frequent indication of foam dressings, in practice, it is clear that foam covers are not more effective than other traditional dressings (Singer, Tassiopoulos & Kirsner, 2017).

The advanced wound treatment strategy to improve the quality of the healing process includes new hydrogel formulations. Some cell hydrogel-based skin substitutes - fibroblasts, keratinocytes - cultured in collagen hydrogel are

indicated for wounds with difficult healing (Kim et al., 2019). As the hydrogel covers promote the absorption of the exudates, and their constitution in three-dimensional networks makes it possible to load drugs, this turned attention to the use of the hydrogel of response to the pH of the calcium alginate (CaAlg) loaded with nanoparticles protomine (NP) and hyaluronic oligosaccharides, with the potential to reduce the chronic inflammatory process induced by bacteria in the wound bed and consequently accelerate wound healing (Wang et al., 2019).

For wounds with abundant exudate, always choose an absorbent dressing, such as calcium alginate, and for dry wounds a moisturizing dressing, such as hydrogel. These are accessible, economical and have an excellent acceptance by users. The wet dressing should not come into contact with the integral perilesional area, because it causes maceration of healthy tissue, increasing the size of the wound (Jones & Foster,2018).

The coverage with nano crystalline silver does not have an affordable cost for most patients and/or public health services. It is, however, a coverage with an innovative and revolutionary technology, indicated for venous lesions (Iljas, Röhl & McGovernSingh,2020, Kapoor & Gupta, 2020) (table1). Nanoparticle silver is a potent antibacterial agent, combating resistance to antibiotics, in treatment of wounds (Silva et al., 2018). Silver coverage can decrease bacterial contamination, however prolonged use can prevent healing (Jones & Foster,2018).

Growth factors are proteins that activate proliferation promoting angiogenesis, mitogenesis and gene transcription, and accelerating healing (Masi et al., 2016, Park, Hwang & Yoon,2017). Growth factors are indicated when the lesion does not respond to traditional treatments, a 30% reduction for venous lesions in the lower limbs and 50% for diabetic lesions, starting from the beginning of treatment for 30 days, as it is a high-cost therapy and those who receive it need follow-up by a wound specialist (Singer, Tassiopoulos & Kirsner, 2018). The influence of growth factors was investigated in the healing of cutaneous wounds in rats. The healing process is accelerated with the use of growth factors, promoting greater angiogenesis, fibroplasia, and collagen maturation (Masi et al., 2016). Insurance companies have begun to accept advanced adjuvant therapies for some conditions, neuropathic, diabetic ulcers (growth factors: REGRANEX, BECAPLASMIN GEL - platelet derivative - PDGF) (Han & Ceilley, 2017).

Covers with natural product – Propolis

In recent years, there has been an increase in the importance of incorporating natural products to coverings to treat skin lesions. Many studies are being developed aiming at the use of biopolymers to replace those that are not produced from renewable sources, and therefore are not biodegradable, damaging the environment; additionally, they present lower costs and toxicity when compared to the synthetic products used in these treatments (Orrego, Fuentealba & Zuñige-Hernández, 2019). In industrialized countries a large portion of the population has used some natural product, with the aim of taking care of their health, at least once in their lives (Pineda et al., 2018).

Voss et al. (2018) carried out an experiment in diabetic rats with lesions, to investigate the possibility of introducing a new advanced and ecological therapeutic approach, aimed at accelerating the healing process of these types of lesions. Natural products, such as polysaccharide-based film loaded with vitamin C (L- ascorbic acid) and propolis (Cel-PVA / VIT C / PROP.) were used in the study. The experiment demonstrated that the bacteria present in the bed of the lesions had a reduction, including bacteria, Escherichia coli and Staphylococcus aureus, and that the healing process was accelerated when compared with the control group.

Propolis can be characterized as a biomaterial with antibacterial properties that combat the formation of biofime, which is responsible for delaying the tissue repair process in the lesion. Propolis can also be an adjuvant treatment to accelerate the fight against antibiotic-resistant organisms. Despite the positive role of propolis in wound healing, some gaps need to be filled: standardization of the chemical composition of propolis, dose, and adverse effects (Oryan, Alemzadeh & Moshiri, 2018).

Red propolis has a higher index of flavonoids in its composition when compared to green and brown propolis. Studies show that lesions treated with red propolis have a greater acceleration of the healing process and that this is directly related to the higher flavonoid index of this biomaterial (Correia et al., 2017). Pinocembrine is the flavonoid considered a marker of brown propoli,s and it has biological activities such as antibacterial, antifungal, antioxidant, anti-inflammatory, anticancer and hypogicemiant (Pineda et al., 2018).

The use of propolis as a complementary treatment has been an important strategy with the ability to improve and promote the healing of wounds in diabetic feet based on its anti-inflammatory and antioxidative properties. In experiments with propolis spray with a concentration of 3% propylene glycol (Beepolis R), an increase in the deposit of collagen and connective tissue was observed favoring the wound closure process (Orrego, Fuentealba & Zuñige-Hernández, 2019).

Propolis used as an adjuvant therapeutic management can accelerate the healing process and improve the inflammatory parameters of different types of wounds. In this experiment, 5% propolis ointment was used twice a day, for four weeks to treat diabetic foot injuries. There was a decrease in the lesion area and the healing process was improved; however, complementary studies to confirm the results of this study and elucidate the treatment time and dose necessary to effectively treat diabetic foot injuries, should be encouraged (Afkhamizadeh et al.,2018).

Propolis can be used to prevent the chronicity of the lesion since it eliminates the infection and the formation of biofilm in the lesion, consequently promoting epithelialization and wound closure. Propolis was also evaluated for its immunosuppressive, immunostimulating, and antioxidant properties, which were shown to be present (Orrego, Fuentealba & Zuñige-Hernández, 2019).

Table 1. Types of coverage currently available on the market.

Coverage	Benefits / disadvantages	Recommendation	Reference
Hydrogel	High absorptive power, keeps the environment moist, facilitates autolytic debridement, and cellular hydration; It can be used in the various stages of healing, including the granulation phase; It can remain up to 3 days on the injury, reducing the trauma of daily change; The amorphous gel form can be used in cavity lesions with devitalized and/or necrotic tissue; Low cost.	Indicated for clean superficial lesions - lacerations, cuts, abrasions; Diabetic injuries, pressure ulcers; Lower limb injury.	(Singer,Tassiopoulos &Kirsner, 2017, Silva et al., 2018).
Hydrocolloids	Promotes hydration of the environment, autolytic debridement and protection of nerve endings, can be used to fill cavities; 1ffers bacterial barrier; It can remain on the injury for one to seven days, avoiding trauma by daily change.	Dry lesions; Lesions with little or medium exudate; Lesions with necrosis or without necrosis.	(Han et al., 2017, Singer,Tassiopoulos &Kirsner, 2017)
Hydrofiber	High and vertical absorption of exudate, promotion of humid environment; traps microorganisms in its fibers; It has a tape presentation for cavities.	Lesions with moderate or high levels of exudate.	(Silva et al., 2018)
Hydrofiber with ionic silver (hydrofiber Ag)	Broad spectrum of effectiveness against injury pathogens; Prophylactic microbicidal agent; the silver is released continuously and controlled inside the cover for up to 14 days.	Lesions with a signficant amount of exudate, infected, and intensely colonized.	(Barnea, Weiss & Gur, 2010, Wilson, Gillen & Hughes,2018)
Calcium Alginate	Great absorptive power, maintaining a humid environment, allows gas exchange, antibacterial barrier, promotes healing (granulation); It should not be used on dry wounds. Requires secondary coverage. Low cost.	Indicated for superficial, cavitary toning lesions - - or with partial loss of tissues; Deep lesions or with a significant amount of exudate and odour.	(Jones, Foster & Longaker, 2018, Wang et al., 2019)
Calcium Alginate / Ionic Silver / Ag	Control of the flora of microorganisms - bacteria and fungi - including strains resistant to antibiotics; Ability to eliminate microorganisms Requires moisture to be used.	Chronic injuries; Lesions infected with moderate to high levels of exudate.	(Wang et al.,2019)
Foam	The inner layer has an absorbent action, the outer layer protects the injured area; Humidity regulator and favours autolytic debridement; Some presentations can be cut off; It can stay up to seven days, avoiding the trauma of daily change; It should not be used on dry lesions or those with little exudate; When not transparent, they impair the observation of the lesion;	Open wounds without infection and devitalized tissues. Wounds with exudate and odor; Venous lesions, cavitary lesions / liquid form.	(Jones, Foster & Longaker 2018, Gianino, Miller & Gilmare, 2018)
Silver Foam	It has high absorption power, protects the lesion, and controls the amount of microorganisms in the lesion bed by releasing the silver for seven days.	Chronic lesions, lesions intensely colonized or with signs of infection.	(Rayman et al., 2005, Jones, Foster & Longaker 2018, Lázaro-Martínez, Álvaro-Afonso & Sevillano-Fernández,2019)
Nano crystalline silver	Large surface for antimicrobial activity due to the extremely small size of the silver crystals; Moisture absorption and retention; faster action when in contact with water than common silver. Uses distilled water; Saline decreases the rapid action of this presentation; High cost.	Venous lesions, infected or colonized; Superficial or deep wounds with antiobiotic resistant microorganisms; In lesions with little exudate	(Jones, Foster & Longaker 2018,Silva et al., 2018)
Advanced adjuvant therapy with platelet-derived growth factors (PDGF)	Chemotactic capacity for macrophages and fibroblasts, modulating the inflammatory and antibacterial response; Accelerates the healing of the injury; Requires secondary coverage Do not use on infected lesions and / or osteomyelitis, or on lesions with a large area of necrosis; Contraindication: patients with oncological diseases.	Chronic diabetic injuries; Complex injuries – elderly; Diabetic foot injuries refractory to conventional treatments.	(Masi et al., 2016, Han& Ceilley,2017, Antunes et al., 2019)

Propolis has a wide variety of biological and pharmacological properties, including antimicrobial, antioxidant, anti-inflammatory, immunomodulating, anti-infectious, antifungal, and anticancer (depending on composition and origin). In experiments with diabetes-induced rats, the topical application of propolis helped in the synthesis of collagen mediated by growth factors, accelerating the healing of the lesion (Garrand, Hozzein & Badr, 2017, Puspasari et al., 2018).

Green propolis has been used as a traditional treatment

for many decades and the knowledge acquired over these periods has informed us to move forward with studies that could fill and respond to some gaps related to the healing of complex wounds in diabetics. Pioneering research was carried out using red propolis, similar to green propolis, but with some components at higher concentration such as flavonoids and cinnamic acid, among others, which have an effective antibacterial action. Bacterial cellulose membranes were incorporated into the red propolis extracts. From this association, it was possible to create a new biotechnological cover in order to treat and accelerate the healing process of diabetic wounds. It was evident that, due to the higher concentration of flavonoids, there was an increase in the levels of growth factors (TGF-B), control of prolonged inflammation with reduction of the size of the wound, and complete epithelialization in a short period of time (Picolotto et al., 2019).

OLIVEIRA *et al*. (2019,) based on the knowledge of the effectiveness of the bacterial cellulose membrane (BC) in the treatment of wounds and burns, but aware of the gap when the wound presents infections and also the discomfort of daily exchange, decided to incorporate co-encapsulating propolis in the self-microemulsifying form and to investigate the antibacterial action and the time of this action on the wound. They discovered that for 7 days the propolis markers were present and that the action against Gram positive and Gram-negative bacteria was efficient with the use of this association (BC/PP) in rat wounds. The bacterial membrane associated with propolis (BC/PP) showed an intense pro-inflammatory action when compared to the membrane without propolis. Fibroblasts were recruited to the wound and collagen production occurred, favoring healing. Future studies need to be carried out to clarify the mechanism of action and make possible a future therapeutic option for complex wounds with the convenience of weekly exchange.

New perspectives of coverage / treatments

The LED therapy associated with the natural latex bromembrane (LBM), extracted from the Brazilian rubber tree, is a new treatment that has been applied with excellent results in accelerating the healing process to patients with diabetes mellitus with injuries in diabetic rats**.** LED therapy has shown the same properties as laser therapy, with the advantage of having a lower cost and the possibility of carrying out this treatment in the Health System (Nunes et al., 2016, Leite et al., 2020).

In recent years, several studies have been carried out to revalidate the efficacy of platelets in chronic wound treatments resistant to other traditional interventions. Platelets are rich in growth factors that promote the formation of new tissues, and interfere with the inflammatory and antibacterial process due to the chemotactic action on macrophages and fibroblasts. The homologous platelet gel was tested in a clinical trial with diabetic patients and with foot injuries. Regarding the process and speed of healing of lesions in diabetic feet, the results showed high rates in most patients. It was found that patients with better and faster results in relation to the healing of the lesion adhered to the care with adequate diet, control of hyperglycemia, rest, and physical activity, when possible (Antunes et al., 2019).

The topical use of 1% valsartan gel (angiotensin beta-blocker) in complex diabetic wounds of elderly mice showed that there was an acceleration of healing with total wound closure in a short period, in addition to improved healing quality, and increased the tensile strength of the scar structure. These properties were attributed to the increased blood flow in the lesion and the increased collagen deposition. This experiment was validated in the swine model (Abadir et al., 2018).

The association of chitosan nanoparticles loaded with curcumin (Cur-CS-NP) was applied to lesions of diabetic rats in order to attenuate the inflammation mediated by macrophages and thus accelerate the formation of new vessels, positively interfering in the acceleration of the healing process. The results of this analysis were promising in relation to the already known properties of curcumin (anti-inflammatory, anti-infective and antioxidant). Curcumin is one of the main additives of MERIC, which has been accredited by the US Food and Drug. However new studies must be carried out to ascertain the association with chitosan and the actions in other cells that participate in the healing phases (Li et al., 2019).

Another new technology was the incorporation of Rubidium to the Calcium Alginate - composing the Rb-CA gel, for the first time with the objective of making possible the production of a new and effective dressing to cure complex lesions such as infected diabetic wounds that need an agent that acts in the control of the microbiota present in these cases. The experiment demonstrated the inhibition of the growth of two species of bacteria, Staphylococcus aureus and *Pseudomonas aeruginosas*, non –toxicity, while also helping to improve neovascularization, re-epithelialization, and the deposit of collagen in the wound environment. The Rb-CA gels also promoted the migration of fibroblasts and keratinocytes, during *in vivo* experimental model of wounds, in type 2 diabetic rats. The gel 100Rb-CA, when compared with the 50Rb-CA and the control group, presented better results. Burn, thermal and chemical wounds also showed improvement in the healing process with this new proposal (He et al., 2019).

Conclusion

This review article sought to include studies that present the characteristics, composition, and action of the additives that make up the coverage indicated for various types of injuries. In addition, presenting proposals with coverage with a natural product - Propolis, which often proves to be an ecological and low-cost option, however there is a need for standardization of extracts. As well, prospects for new treatments, and coverage with incorporations of natural products and new technologies that have demonstrated high efficiency and safety, but that require further studies, were presented. Interventions in patients with injuries must be preceded by a general approach on the underlying pathology, present comorbidities, nutritional, and psychosocial assessment. The cost/benefit analysis is a necessary consideration due to the high cost of many coverages; however, it is important to keep in mind that the exchange

interval is shorter. There is no single cover that can be used at all stages of a wound healing process, so providing effective care to users with injuries is a challenge for the health team, especially for nurses who must be aware and recognize the stage of the injury and the factors present that hinder the healing process, to effectively choose the appropriate coverage.

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References

Abadir, P., Hasseini, S., Faghih, M. et al. Topical Reformulation of Valsartan for Treatment of Chronic Diabetic Wounds. *J. Invest. Dermatol.*, (2018). Doi: 10.1016/j.jid.2017.09.030

Afkhamizadeh, M., Aboutarabi, R., Ravari, H. et al. Tropical propolis improves wound healing in patients with diabetic foot ulcer a randomized controlled trial. *Nat Prod Res.*, 32:17, 2096 – 2099, (2018). Doi: 10.1080/14786419.2017.1363755.

Ahmed, A., Getti, G., Boateng,J. Ciprofloxacin-loaded calcium alginate wafers prepared by freeze-drying technique for potential healing of chronic diabetic foot ulcers. *Drug Deliv. and Transl. Res.*, 8:1751–1768, (2018). https://doi.org/10.1007/s13346-017-0445-9

Almeida, V.C.D., Araújo, S.T., Negreiros, F.D.S. et al. Complicações microvasculares e macrovasculares em pessoas com diabetes tipo 2, em atendimento ambulatorial. *Rev. RENE*, 18:6, 787-793, (2017).

American Diabetes Association. Classification and Diagnosis of Diabetes. *Diabetes Care*,40 (suppl.1),S11-S24, (2017).Doi.org/10.2337/dc17-S005.

Antunes, M.B., Costa, L., Carneiro, M. et al. Topic Platelet Gel Application in Chronic Diabetic Foot Ulcers. *Diabetes Metab Syndr*, 13, 644–647,(2019).https:// doi.org/10.1016/j.dsx.2018.11.032

Barnea,Y., Weiss,J.,Gur,E. A review of the applications of the hydrofiber dressing with silver (Aquacel Ag®) in wound care. *Ther Clin Risk Manag*.,6: 21–27,(2010).

Correia, F.R.S., Schaneul, F.S., Nunes, N.M., et al. Brazilian red propolis improves cutaneous wound healing suppressing inflammation – associated transcription factor NFkB. *Biomed. Pharmacother*,86, 162-171, (2017).https://dx.doi.org/10.1016/j.biopha.2016.12.018

Dryden, M., Bagneid, M., Eckmann, C. et al.Fisiopatologia e carga de infecção em pacientes com diabetes mellitus e doença vascular periférica: foco em infecções de pele e dos tecidos moles. *Clin. Microbiol. Infect*,21:2017,S27- S32, (2015). https://doi.org/10.101016/j.cmi.2015.03.024

Faludi, A.A.; Izar, M.C.O.; Saraiva, J.F.K.; et al. Diretriz Brasileira baseada em evidências sobre prevenção de doenças cardiovasculares em pacientes com diabetes: Posicionamento da Sociedade Brasileira de Diabetes (SBD), da Sociedade Brasileira de Cardiologia (SBC) e da Sociedade Brasileira de Endocrinologia e Metabologia (SBEM). *Arq Bras Cardiol*.,109: 6(1),0188 , (2017). https://doi.org/10.5935/abc.2017

Fernandes, V.S., Passos, K. S., Oliveira, D. M. de L. et al. Utilização da prata nanocristalina no tratamento de feridas. International Nursing Congress, Maio/2017. Universidade Tiradentes – Unit.

Garrand, O., Hozzein, W.N., Badr, G. Wound, healing: time to look for inteligente, 'natural' immunological approaches? *BMC Immunol.*,18:23, (2017). doi: 10.1186/s12865-017-0207-y

Gianino, E., Miller, C., Gilmare, J. Smart Wound Dressings for Diabetic Chronic Wounds. Bioengineering (Basel), 5:3,E51,(2018). Doi 103390/bioengineering5030051

Kim, H.S., Sun, X., Lee, J.H. et al. Advanced drug delivery systems and articial skin grafts for skin wound heoling. *Adv Drug Deliv Rev*.,146, 209-239, (2019).

Han, G., Ceilley, R. Chronic Wound Healing: A Review of Current Management and Treatments. *Adv Ther*.,34,599.610,(2017).doi 10.1007/s12325-017-0478-y. October/2017.

He, X., Ding, Y., Xic, W. et al. Rubidium Containing Calcium Alginate Hidrogel for Antibacterial and Diabetic Skin Wound Healing Applications. *ACS Biomater. Sci. Eng.*, 5, 4726-4738, (2019). Doi: 10.1021/acsbiomaterials.9b00547

Heidemann, C., Paprott, R., Stühmann, L.M., et al. Perceived diabetes risk and related determinants in individuals with high actual diabetes risk: results from a nationwide population-based survey. *Bmj Open Diab Res Ca.*, v7:1, e000680, (2019). Doi: 10.1136/bmjdrc-2019-000680

Huang, Q.; Xiong, H.; Yan, P.; et al. Extracorporeal Shok Wave Therapy for Treating Foot Ulcers in Adults with Type 1 and Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized ControlledTrials. *Can J Diabetes*,44,196-204, (2020). DOI: 10.1016/j.jcjd.2019.05.006

Iljas, J.D., Röhl, J., McGovern,J.A. A human skin equivalent burn model to study the effect of a nanocrystalline silver dressing on wound healing. *Burns*,(2020). https://doi.org/10.1016/j.burns.2020.07.007

International Diabetes Federation (IDF). Diabetes Atlas, 9th Edition, IDF, Brussels, Belgium. 2019. Available in: https://www.diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf

Jarbrink, K., NI,G.; Sonnergren, H.; Schmidtchen, et al. Prevalence and Incidence of Chornic Wounds and related Complications: A Protocol for a Systematic Rewiew. *Syst. Rev*, 5, 152, (2016). Doi: 10:1186/s13643-016-0329-y

Jeon, M., Kim,S.Y. Application of a paste-type acellular dermal matrix for coverage of chronic ulcerative wounds. *Arch Plast Surg*., 45(6), 564–571, (2018). 10.5999/aps.2018.00605

Jones, R.E., Foster, D.S., Longaker, M.T. Management of Chronic wounds-2018.*JAMA*,320:14,1481-1482,(2018). doi:10.1001/jama.2018.12426

Jude, E. B., Apelqvist, J.,Spraul, M. Prospective randomized controlled study of Hydrofiber® dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers. *Diabet Med*, (2007). https://doi.org/10.1111/j.1464-5491.2007.02079.x

Lázaro-Martínez,J.L., Álvaro-Afonso, F.J., Sevillano-Fernández,D. Clinical and Antimicrobial Efficacy of a Silver Foam Dressing With Silicone Adhesive in Diabetic Foot Ulcers With Mild Infection. *Int J Low Extrem Wounds*, (2019). https://doi.org/10.1177/1534734619866610

Leite, M.N, Leite, S.N., Caetano, G.F. et al. Healing effects of natural latex serum 1% from *Hevea brasiliensis* in an experimental skin abrasion wound model. *An Bras Dermatol.*, 95:4, 418-427,(2020). https://doi.org/10.1016/j.abd.2019.12.003

Li, F., Shi, Y.. Liang, J.I.A. et al. Curcumin-loaded chitosan nanoparticles promote diabetic wound healing via attenuating inflammation in a diabetic rat model. *J. Biomater. Appl.*,34:4, 476-486, (2019). Doi: 10.1177/0885328219860929

Mariam, T.G, Alemayehu,A, Tesfaye,E. et al. Prevalence of Diabetic Foot Ulcer and Associated Factors among Adult Diabetic Patients Who Attend the Diabetic Follow-Up Clinic at the University of Gondar Referral Hospital, North West Ethiopia, 2016: Institutional-Based Cross-Sectional Study. J Diabetes Res.(2017). https://doi.org/10.1155/2017/2879249

Masi,E.C.D.J.D., Campos, A.C.L., Mais, F.D.J.D. et al. The influence of growth factors on skin wound healing in rats. *Braz. j. otorhinolaryngol.* [online].,82:5, 512-521,(2016). https://doi.org/10.1016/j.bjorl.2015.09.011.

Makrantonaki, E., Wlaschek, M., Scharffetter-Kochanek,K. Pathogenesis of wound healing disorders in the elderly. *JDDG*.(2017). https://doi.org/10.1111/ddg.13199

Nunes, G.A.M.de, Reis,M.do C., Rosa, M.F.F. et al. A system for treatment of diabetic foot ulcers using led irradiation and natural latex. *Res. Biomed. Eng.*,32:1,(2016). https://doi.org/10.1590/2446-4740.0744.

Nhim, K., Gruss, S.M., Parterfield, D.S.; et al. Using a RE-AIM framework to identify promising practices in National Diabetes Prevention Program implementation. *Implement Sci* ,14: 81,(2019).https://doi.org/10.1186/s13012-019-0928-9

Oliveira, F.M., Barud, H. da S., Torres, E.C., et al. Development, characterization and pre-clinical trials of an innovative wound healing dressing based on propolis (EPP-AF R) – containing self-microemulsifying formulation incorporated in biocellulose membranes. *Int. J. Biol. Macromol.*, 136, 570-578,(2019). https://doi.org/10.1016ijbiomar.2019.05.135

Orrego, V.M.R., Fuentealba, E.L.,Zuñige-Hernández, J. Propolis as Adjuvant in the Healing of Human Diabetic Foot Wound Receiving Care in the Diagnostic and Treatment Centre from Regional Hospital of Talca. Clinical Study. *J Diabetes Res.*,(2019). https://doi.org/10.1155/2019/2507578

Oryan, A., Alemzadeh, E., Moshiri, A. Potencial role of propolis in wound healing: Biological properties and therapeutic activities. *Biomed. Pharmacother.*, 98, 469-

483,(2018).https://doi.org/10.1016/j.biopha.2017.12.069.
Park,J.W., Hwang,S.R., Yoon,I. Advanced Growth Factor Delivery Systems in Wound Management and Skin Regeneration. *Molecules*,22, 1259,(2017) doi:10.3390/molecules22081259
Pereira, S.G., Moura, J., Carvalho, E. et al. Microbiota of Chronic Diabetic Wounds: Ecology, Impact, and Potential for Innovative Treatment Strategies. *Front Microbiol.*, 21, (2017).
Pineda, J.G., Uribe-Uribe, N., López-Garcia,P. et al. Effect of pinocembrin isolated from Mexican brown propolis on diabetic nephropathy. *Molecules*, 23:4, (2018).
Picolotto, A., Pergher, D., Pereira, G.P. et al. Bacterial Cellulose Membrane associated with red propolis as phytomodular : Improved healing effects in experimental models of diabetes mellitus. *Biomed. Pharmacother*, 112,108640,(2019).https://doi.org/10.1016/1biopha.2019.1086-40
Puspasari, A., Harijanti, K., Soebadi, B. et al. Effects of topical application of propolis extract on fibroblast growth factor-2 and fibroblast expression in the traumatic ulcers of diabetic Rattus Norvegicus. *J Oral Maxillofac Pathol.*,22, 54-58, (2018).Doi: 10.4103/jomfp.JOMFP_82_17:10.4103/jomfp.JOMFP_82_82_17
Rayman, G., Rayman, A., Baker, N., et al. Sustained silver-releasing dressing in the treatment of diabetic foot ulcers. *Br J Nurs.* 14(2), 109-114,(2005).doi:10.12968/bjon.2005.14.2.17441
Ravazzani, A.C., Micali, A.C.P., Lemos, D.; et al. Risco de úlceras de membros inferiores nos diabéticos de um ambulatório universitário. *Rev. Méd. UFPR*,3:2, (2016).
Shoham, Y., Krieger,Y., Tamir, E. Bromelain-based enzymatic debridement of chronic wounds: A preliminary report. *Int Wound J.*,(2018). https://doi.org/10.1111/iwj.12925
Singer, A. J., Tassiopoulos, A., Kirsner, R. Evaluation and Management of Lower-Extremity Ulcers. *N Engl J Med*., 377:16, 1559-1567, (2017).
Singh,B., Kapoor,S., Gupta, A.K. Comparingthe efficacy of nano crystalline silver dressing versusbetadine dressing in management of diabetic foot ulcer. *Int Surg J.*,7(5):1424-1430,(2020).
Silva, M.M.P.S., Aguiar, M.I.F., Rodrigues, A.B. et al. The use of nanoparticles in wound treatment: a systematic review. *Rev Esc Enferm USP*., 51, (2018). https://doi.org/10.1590/s1980-220x2016043503272
Sociedade Brasileira de Diabetes. Diretrizes Sociedade Brasileira de Diabetes 2019-2020. Available in: file:///C:/Users/Andressa%20Bethune/Downloads/42638-Article%20Text-144216-1-10-20200317.pdf
Tan, H.Q.M., Chin, Y.H., Ng,C.H. et al. Multidisciplinary team approach to diabetes. An outlook on providers' and patients' perspectives. *Prim Care Diabetes.* 14:5,(2020). https://doi.org/10.1016/j.pcd.2020.05.012
Verhulst, M.J.L., Loos, B. G., Gerdes, V. E. A., Teeuw, W.J. Evaluating All Potential Oral Complications of Diabetes Mellitus. *Front. Endocrinol*,10: 56,(2019). Doi: 10.3389/fendo.2019.0056
Voss, G.T., Gularte, M.S., Vogt, A.G. et al. Polysaccharide-based film loaded with vitamin c and propolis: a promising device to aceelerate diabetic wound healing. *Int. J. Pharm.*,552,340–351, (2018).https://doi.org/10.1016/j.ijpharm.2018.10.009.
Wang, T., Zheng, Y., Shi, Y. et al. pH – responsive calcium alginate hidrogel laden with protamine nanoparticles and hyaluronan oligosccharide promotes diabetic wound healing by enhancing angiogenesis and antibacterial activity. *Drug Deliv. Transl. Res*., 9, 227-239, (2019).https://doi.org/10.1007/s13346-018-00609-8
Wilson,P., Gillen,C.,Hughes,M. A clinical case series on the effectiveness of an enhanced ionic silver hydrofiber dressing in the management of diabetic foot ulceration. *Diabet. Foot. J.*, 21(4), 239 – 46,(2018).
Xiao, Y., Reis, A. L., Feric, N. et al. Diabetic wound gereneration using peptide-modified hydrogels to target re-epithelialization. *PNAS*, 4:113, E5792-E5801,(2016). www.pnas.org/cgi/doi/10.1073/pnas.1612277113
Zheng, Y., Ley, H. S., Hu, F.B. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol.*,14:2,88-98, (2018). Doi: 10.1038/nrendo.2017.151 PMID 29219149