








USE OF THE HUMAN PLACENTA IN THE HEALING OF FOOT ULCERS IN PEOPLE WITH DIABETES: INTEGRATIVE REVIEW

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ABSTRACT

Objective: To identify in the literature the contributions of the use of the human placenta in the healing of foot ulcers in people with diabetes. **Method:** An integrative review study carried out by searching articles in Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Scientific Electronic Library Online (SciELO), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, National Library of Medicine (PubMed), Web of Science and Scopus, using the search strategies: Placenta AND “Diabetic foot” and Placenta AND “Diabetic Foot”. **Results:** The initial search resulted in 148 articles. After applying the inclusion and exclusion criteria, a final sample of 12 articles was obtained. It was observed that the placenta has the potential to promote the improvement of granulation tissue and peripheral circulation, greater epithelialization, and reduction in the wound area, with the majority use of cryopreserved placental and amniotic membrane allograft. **Conclusion:** The human placenta is a nutrient-rich biological material that has the potential to contribute to the tissue repair of foot ulcers in people with diabetes in a shorter period of time.

DESCRIPTORS: Placenta. Diabetic foot. Wound healing. Enterostomal therapy.

UTILIZAÇÃO DA PLACENTA HUMANA NA CICATRIZAÇÃO DE ÚLCERAS NOS PÉS DE PESSOAS COM DIABETES: REVISÃO INTEGRATIVA

RESUMO

Objetivo: Identificar na literatura as contribuições da utilização da placenta humana na cicatrização de úlceras nos pés de pessoas com diabetes. **Método:** Estudo de revisão integrativa realizado por meio da busca de artigos na Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Scientific Electronic Library Online (SciELO), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, National Library of Medicine (PubMed), Web of Science e Scopus, com a utilização das estratégias de busca: Placenta AND “Pé diabético” e Placenta AND “Diabetic foot”. **Resultados:** A busca inicial resultou em 148 artigos. Após aplicação dos critérios de inclusão e exclusão, obteve-se amostra final de 12 artigos. Observou-se que a placenta tem potencial de promover a melhora do tecido de granulação e a circulação periférica, maior repitelização, redução na área da ferida, com uso majoritário de aloenxerto de membranas placentária e amniótica criopreservadas. **Conclusão:** A placenta humana é um material biológico rico em nutrientes que apresentou potencial para contribuir com o reparo tecidual de úlceras nos pés de pessoas com diabetes em menor período de tempo.

DESCRIPTORES: Placenta. Pé diabético. Cicatrização. Estomaterapia.

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USO DE LA PLACENTA HUMANA EN LA CICATRIZACIÓN DE LAS ÚLCERAS DEL PIE EN PERSONAS CON DIABETES: REVISIÓN INTEGRADORA

RESUMEN

Objetivo: Identificar en la literatura las contribuciones del uso de la placenta humana en la cicatrización de las úlceras del pie en personas con diabetes. **Método:** Estudio de revisión integradora, realizado mediante búsqueda de artículos en LILACS, SCIELO, CINAHL, Cochrane Library, PubMed, Web of Science y Scopus, utilizando las estrategias de búsqueda: Placenta AND "Diabetic foot" y Placenta AND "Diabetic Foot". **Resultados:** La búsqueda inicial resultó en 148 artículos. Tras aplicar los criterios de inclusión y exclusión, se obtuvo una muestra final de 12 artículos. Se observó que la placenta tiene el potencial de promover la mejoría del tejido de granulación y circulación periférica, mayor reepitelización, reducción del área de la herida, con uso mayoritario de aloinjerto de placenta y membrana amniótica criopreservados. **Conclusión:** La placenta humana es un material biológico rico en nutrientes que tiene el potencial de contribuir a la reparación tisular de las úlceras del pie en personas con diabetes en un período de tiempo más corto.

DESCRIPTORES: Placenta. Pie diabético. Cicatrización de heridas. Estomaterapia.

INTRODUCTION

The human placenta and its derivatives (umbilical cord, placental disc, sac and amniotic fluid) are privileged immune tissues, with a complex composition of extracellular matrix rich in nutrients, growth factors and cytokines involved in cell growth, survival and modulation of inflammation¹.

In view of these particular characteristics, placenta has been successfully used for the treatment of difficult-to-heal wounds, such as diabetes mellitus (DM) ulcers¹⁻³. This is a relevant finding, given that neuropathic ulcers caused by DM are a serious and costly complication for the Brazilian National Health System. The prevalence of people with foot ulcers caused by DM is estimated to be higher than 6% worldwide, which causes several non-traumatic lower limb amputations⁴.

In conventional treatment for foot ulcers in people with DM, cleaning of the wound bed, debridement of devitalized tissues, management of circulation, application of topical dressings and infection control are commonly performed. However, in some ulcers, conventional treatment alone is insufficient to achieve tissue repair in a satisfactory timeframe^{5,6}.

Thus, recent clinical studies indicate that the use of human placenta promotes benefits in the tissue repair of foot ulcers in people with DM. Currently, there is already ongoing research that seeks to improve techniques for the preservation of placental tissues and derivatives for their use as a new type of biological dressing^{7,8}.

Although the studies agree with the use of human placenta and its derivatives in the treatment of ulcers in people with DM, in general, health institutions in Brazil that care for pregnant women discard the placenta soon after birth as solid hospital waste, because it is subgroup A4 of infectious waste⁹. This demonstrates the relevance of new studies on the subject, with the intent of providing information about the use of this biological material and arouse new original studies.

Given the above, it is found that the contributions and benefits of placental tissue in tissue repair in difficult-to-heal ulcers, such as ulcers in people with DM, need to be determined to stimulate their reproducibility, in addition to building and validating protocols for clinical practice, new ways of purifying placental derivatives, and isolating healing compounds.

The justification for this study is based on the need to provide the use of low-cost and more biodegradable materials, such as human placenta, which, despite being discarded after birth, can be processed and used as a biological dressing.

This study aimed to identify in the literature the contributions of the use of human placenta in the healing of foot ulcers in people with diabetes.

METHODS

This is an integrative review study that methodically went through six stages:

- Construction of the research question;
- Search, screening and selection of studies;
- Extraction of the sample findings;
- Critical analysis of the sample;
- Construction of the results;
- Presentation of the review¹⁰.

To conduct the study, the guiding research question was: “What are the contributions of the use of human placenta in the healing of foot ulcers in people with diabetes?” The guiding question was constructed based on the PICO strategy, an acronym that stands for:

- P = patient (people with diabetes and foot ulcers);
- I = intervention (use of human placenta as an adjunct to treatment);
- O = outcome (progress in healing).

The element C, which refers to comparison, was not used because of the review category¹¹. The search for scientific production on the theme was conducted in the period January and February 2022. The Periodical Portal of the Coordination of Improvement of Higher Education Personnel (CAPES) was used, using the Federated Academic Community (CAFe) of the University of São Paulo, to search for scientific documents in Latin American and Caribbean Health Sciences Literature (LILACS), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scientific Electronic Library Online (SciELO), Cochrane Library, National Library of Medicine (PubMed), Scopus, Cochrane Library, and Web of Science.

To perform the search, we used controlled descriptors from the Medical Subject Headings (MeSH) and the Health Sciences Descriptors (DeCS), defined to reach the articles on the theme of interest, in association with the Boolean operator “AND,” as shown in Table 1.

Table 1. Search strategy for the articles. Redenção (CE), Brazil, 2022.

Databases	Search strategy
LILACS and SciELO	Placenta AND “Pé diabético”
PubMed, Web of Science, CINAHL, e Scopus	Placenta AND “Diabetic foot”

Source: Elaborated by the authors, 2022.

Original studies that answered the guiding question were selected. There was no restriction on publication year or language. Duplicates, in vitro or animal studies, editorials, review studies, abstracts (preprint), meeting abstracts, clinical trial protocols, and case series were excluded.

Two researchers carried out the screening and selection of the scientific articles independently. The articles found in the databases were analyzed for duplicate titles, keeping only one version of each article. After excluding the duplicates, we proceeded with the judgment of the theme and type of study, by reading the titles and abstracts. Then, the eligibility of the scientific documents was evaluated by reading them in their entirety.

The extraction of the main findings from the scientific documents was made with the help of a data collection tool¹², and these findings were analyzed and synthesized, with subsequent organization into tables.

RESULTS

After applying the search strategy, 148 articles accessible in international databases were found. In LILACS and SciELO, no studies on the theme were found. Through duplicate analysis, 71 repeated articles were excluded.

In the analysis of the theme and type of study, studies that did not fit the inclusion criteria were excluded ($n = 65$). Subsequently, the eligibility of the articles was considered by reading the studies in their entirety ($n = 12$), with an appreciation of the methodological rigor.

The 12 articles reviewed were able to meet the study objective and were included in the final sample. The screening and selection pathway is described in the flow chart in Fig. 1, as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) of 2020.

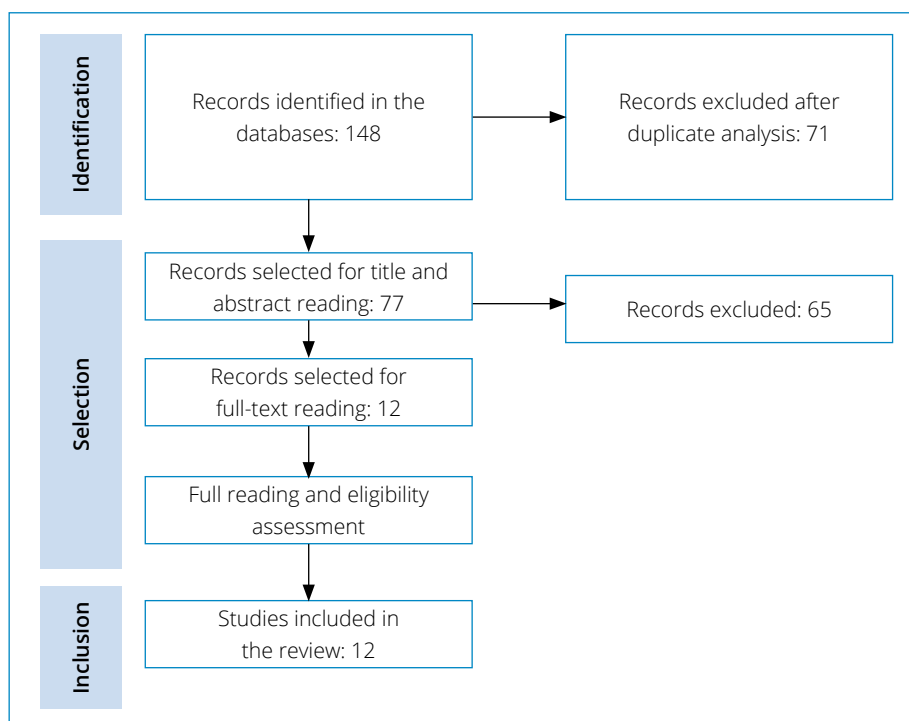


Figure 1. Flowchart of identification, selection and inclusion of studies according to PRISMA (2020). Redenção (CE), Brazil, 2022.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Source: Prepared by the authors.

The 12 articles included in the review aimed to identify the contributions of the use of human placenta and its derivatives in the treatment of foot ulcers from diabetes. Participants ranged from 15 to 1,622 patients in each study. In eight scientific articles the participants were allocated to two different analysis groups, with standard treatment and experimental treatment^{3,13-19}. The others used only human placenta, with no comparison treatment²⁰⁻²³.

There was a predominance in the use of human placental membrane allograft and human amniotic membrane allograft as standard of care. The predominant method for preservation of biological tissues and placental-derived cells was cryopreservation. Healing of the treated ulcers occurred from four to 36 weeks by treatment applications ranging from one to 11 applications.

To evaluate the progress of tissue repair, the measurement of wound size and amount of exudation, weekly photographic recording, and the application of Wagner's classification scale and biomarkers were performed. Regarding the contributions of the placenta, greater progression of the tissue repair process, improvement of granulation tissue and peripheral circulation, greater reepithelialization, reduction in wound area and decrease in infection were identified.

The presentation of the results of this review included a brief characterization of the primary studies, summarized in Tables 2 and 3, and a subsequent descriptive synthesis of the theoretical and methodological aspects of the articles.

Table 2. Characterization of the studies included in the integrative review. Redenção (CE), Brazil, 2022.

Authors/year/country	Objective	Sample	Study type
Zelen et al., 2013 ¹³ United States	Compare the healing characteristics of foot ulcers treated with dehydrated human amniotic membrane allograft versus standard treatment.	n=25	Randomized clinical trial
Werber e Martin, 2013 ²⁰ United States	To evaluate the representativeness of granulated amniotic membrane and amniotic fluid as a useful option for the treatment of chronic diabetic foot wounds	n=20	Prospective study
Lavery et al., 2014 ¹⁷ United States	To evaluate the efficacy and safety of Grafix (a viable human wound matrix) compared to standard wound care to treat chronic diabetic foot ulcers	n=97	Randomized clinical trial
Frykberg et al., 2017 ¹⁴ United States	Investigate the ability of cryopreserved human placental membrane in promoting diabetic foot healing with exposed bone and tendon	n=27	Randomized clinical trial
Wu et al., 2017 ²¹ China	To evaluate the safety of human placental-derived mesenchymal cells at term in patients with peripheral arterial disease and foot ulcers in people with diabetes	n=15	Multicenter, dose escalation study
Ananian et al., 2018 ¹⁵ United States	Investigate the clinical outcomes of cryopreserved human placental membrane and human fibroblast-derived dermal substitute for the treatment of diabetic foot	n=62	Randomized clinical trial
Raspovic et al., 2018 ¹⁶ United States	To evaluate the efficacy of cryopreserved viable placental membrane for the management of diabetic foot	n=360	Randomized clinical trial
Pacaccio et al., 2018 ²² United States	To evaluate the safety and efficacy of chorioamniotic used as a foot ulcer dressing in patients with diabetes	n=63	Multicenter, prospective study
Sabolinski and Capotorto, 2019 ¹⁸ United States	To evaluate the comparative effectiveness of a human fibroblast-derived dermal substitute to a cryopreserved viable placental membrane for the treatment of diabetic foot ulcers in real-world scenario settings	n=1.622	Retrospective analysis study
Swoboda, 2021 ²³ United States	To evaluate the clinical use and outcomes of cellular and/or viable human amniotic tissue-based products with live mesenchymal stem cells used to treat chronic wounds in the outpatient clinic of a community hospital, with the goal of comparing real-world product use and outcomes with the use and outcomes described in the chronic wound literature	n=89	Retrospective study
Meamar et al., 2021 ³ Iran	To evaluate the efficacy of nanofibers containing human placental-derived mesenchymal stem cells with or without platelet-rich plasma for diabetic foot healing	n=28	Pilot clinical trial
Chisari et al., 2021 ¹⁹ Italy	To evaluate the efficacy of human amniotic membrane in individuals with diabetic foot	n=16	Retrospective study

Source: Prepared by the authors, 2022.

Table 3 presents relevant characteristics of the studies on how placenta is used and managed to treat ulcers and the main results evidenced in the studies.

Table 3. Distribution of the use and management of placenta for treatment of diabetic foot and the main results. Redenção (CE), Brazil, 2022.

Authors	Form of use/ application of the placenta	Application protocol	Main result
Zelen et al., 2013 ¹³	Dehydrated human amniotic membrane allograft	A weekly application with a nonadherent dressing and a hydrogel foam	After four weeks of application of the dehydrated human amniotic membrane allograft, there was a 92% healing rate and 32% wound reduction.
Werber e Martin, 2013 ²⁰	Cryopreserved human amniotic membrane and amniotic fluid allograft	Administration at 14-to-21-day intervals until the wound is declared healed or the planned observation period (12 weeks) is over	Granulated amniotic membrane and amniotic fluid represented a useful option for the treatment of diabetic foot wounds. Of the 20 patients, 90% demonstrated complete tissue repair after 12 weeks observation and none of the patients required amputation
Lavery et al., 2014 ¹⁷	Viable human membrane matrix	Application once a week (± 3 days) for up to 84 days. Cleaning and surgical debridement of the lesions were performed weekly. In addition, non-adherent dressings and viable human membrane matrix were used to fully contact the lesion and the edges	Of the 50 participants, 31 patients who received Grafix achieved a 50% reduction in lesion size. The average time to lesion closure was 42 days. The highest probability of healing occurred at 12 weeks. Follow-up every four weeks for 12 additional weeks showed that the ulcers remained closed in 82.1% of the patients. In addition, there were fewer lesion-related infections (nine of 50 patients) compared to standard treatment (17 of 47).
Frykberg et al., 2016 ¹⁴	Cryopreserved human placental membrane allograft	Weekly application for 16 weeks	Complete wound granulation at week 16 was achieved by 96.3% of the patients in an average of 6.8 weeks. Complete wound closure occurred in 59.3% (average of 9.1 weeks). The four-week reduction in area was 54.3%. There were no adverse events related to the product. Only two participants required surgical intervention.
Wu et al., 2017 ²¹	Intramuscular formulation of mesenchymal cells derived from human placenta at term	Intramuscular formulation of 3×10^6 , 10×10^6 , 30×10^6 and 100×10^6 cells, administered intramuscularly to the ulcerated limb on days one and eight of the study, in combination with standard treatment	There were indications of ulcer healing after treatment, along with increased peripheral circulation and decreased biomarker of vascular injury.
Ananian et al., 2018 ¹⁵	Cryopreserved human placental membrane allograft	Weekly treatment of up to eight applications or until complete wound closure, with cryopreserved viable placental membrane of size 5×5 cm and 2×3 cm	About 70% of the patients achieved 50% or more reduction in wound area. At the end of treatment, 48.4% of the patients achieved 100% epithelialization.

continue...

Table 3. Continuation...

Authors	Form of use/ application of the placenta	Application protocol	Main result
Raspovic et al., 2018 ¹⁶	Cryopreserved human placental membrane allograft	Four applications of cryopreserved viable placental membrane grafts	End-of-treatment closure was achieved in 59.4% of wounds, with a mean treatment duration of 42 days and four applications of cryopreserved viable placental membrane grafting. The probability of wound closure at week 12 was 71%, and the number of amputations and wound-related infections were 13 (3%) and nine (2%), respectively. There was a > 50% correlation of wound area reduction at week 4 and wound closure at week 12.
Pacaccio et al., 2018 ²²	Human chorioamniotic membrane allograft	11 weekly applications	After 12 weeks, 40% of the foot ulcers achieved complete closure, which varied with lesion size (small lesions showed faster closure).
Sabolinski and Capotorto, 2019 ¹⁸	Cryopreserved viable placental membrane	Average number of 4.63 applications, with an average interval of nine days	The mean depth of the ulcers was 4.5 ± 4.59 , with a mean of 6.43 ± 6.73 cm. Complete closure of these lesions occurred within 36 weeks. About 25% of the patients treated with viable cryopreserved placental membrane received a single application, and 75.8% received multiple applications, with the interval between uses being 14 ± 17.9 days.
Swoboda, 2021 ²³	Viable placental membrane grafts	Application with the average number of 5.6 days associated with a silicone mesh contact layer and secondary dressings, including those with antimicrobial agents. Standard treatment prior to application. Patients with moderate drainage received dressing changes mid-week, with viable placental membrane grafts applied weekly	Participants who experienced healing within 12 weeks received average applications of 4.2 viable placental membrane grafts. Of the patients who received viable membrane graft therapy, 48% (n = 43) received no additional advanced therapy, such as negative pressure, during the study period. The shortest healing time was 16 days, and the longest was 541 days. By 12 weeks, 57% of the wounds had healed.
Meamar et al., 2021 ¹³	Nanofibers seeded with human placenta-derived mesenchymal stem cells	Patients received gelatin nanofibers seeded with human placenta-derived mesenchymal stem cells (group A) or nanofiber dressings loaded with human placenta-derived mesenchymal stem cells after coating the ulcer with platelet-rich plasma gel (group B) twice a week until the ulcer was healed, which was followed for up to 12 weeks	After 12 weeks, patients in the groups that received the human placenta-derived mesenchymal stem cells had a more pronounced reduction in ulcer area compared to the standard treatment group. The reduction in wound size was 66 percent in group A and 71 percent in group B. At 16 weeks, the ulcers in group B reduced by 80%, while in group A it was 54%.
Chisari et al., 2021 ¹⁹	Human amniotic membrane grafting	Before the application, local and systemic antibiotics were administered, and seven days after the last antibacterial administration. After treatment for 20 days with tibiotoxic tobramycin in local therapy, human amniotic membrane grafting was applied for 15 weeks	After 15 weeks, 56.2% of the diabetes ulcers achieved complete resolution and 43.8% achieved partial resolution.

Source: Elaborated by the authors (2022).

DISCUSSION

The findings of the study show consensus regarding the use of human placenta as an adjuvant in the treatment of ulcers in people with DM. The human placenta showed potential to promote reepithelialization and healing in a shorter period of time^{14,15}.

In the studies analyzed there was exclusive use of human placenta. Once well processed, no adverse events or rejections associated with the treatment were recorded. All studies showed beneficial results in the process of tissue repair of foot ulcers with the use of placental tissues. This is due to the fact that placental tissues contain antimicrobial properties, small levels of human leukocyte antigen, and consequently low immunological rejection⁸.

Placenta have been used as injections and nanofibers seeded with mesenchymal stem cells; however, the predominant form of use has been human placental and amniotic membrane allografts. It is hoped that with advances in preservation technologies, placental tissue allografts will become available for commercial use^{3,21}.

The human placental membrane allograft retains extracellular matrix, growth factors, and viable cells beneficial to the healing process of difficult-to-heal wounds in different locations of the body. A study conducted in the United States observed complete healing in 40% of the foot ulcers on the wounds of 63 participants within 12 weeks of using the human placental membrane graft²². Research conducted in Italy corroborated this finding¹⁹.

This result may be associated to the fact that the human amniotic membrane allograft is composed of extracellular matrix and a complex of regulatory cytokines that promote cell proliferation, cell modulation and secretion of cytokines by several cell types that boost tissue repair. It is emphasized that the form of preservation of placental tissues was cryopreservation. This method differs in the temperature required for storage and transport, from -75 to -85°C , and the shelf life is three years if this temperature is maintained. New studies are being developed in order to extend the shelf life of this formulation⁶.

The healing period of the ulcers varied from 4 to 36 weeks. Research in the United States observed that lesions measuring 25 cm^2 required 102 days and 11 applications of human placental membrane allograft for complete closure¹⁶. Another study demonstrated that the use of amniotic membrane in the treatment of ulcers in people with DM achieved complete healing by the end of the 12th week¹⁷. These data demonstrate the effectiveness of using human placenta in progressing tissue repair.

Thus, the application of human amniotic membrane can be seen as a positive intervention procedure in the healing of wounds on the feet of people with DM, taking into account the area of the injury, the manner, form, and time of the required applications. Furthermore, the use of human placenta for research purposes has the advantage of being low cost, since this material is discarded as solid waste after delivery.

Data such as these become extremely important, since scientific innovation research such as that cited used a biodegradable human biological material as a factor in the healing of foot ulcers. Nowadays, in most health institutions, the placenta is still a disposable material. In this perspective, there is an urgent need for a protocol for the use of the placenta that respects the ethical guidelines between the parturient woman and the health professionals, with the objective of using such material for research purposes.

It is worth emphasizing the need to insert into the routine of life of users of this type of treatment the prevention of new injuries and health education, with reference to the importance of daily glycemic and metabolic control, the correct cleaning of the feet, the correct type of shoes and socks, in order to provide a positive result during the entire therapeutic process.

Such findings indicate that the placenta is a therapeutic product that can favor the reduction of the lesion. The tissue repair of a difficult-to-heal ulcer may positively impact quality of life, reduce the risk of falling, improve balance and gait, and thus enable the patient to be more active in their activities of daily living, in addition to minimizing the risks that an infected ulcer can bring to the individual and the financial burden with its treatment.

It is worth pointing out the limitation in the amount of research analyzed on the use of human placenta in diabetic foot tissue repair. Therefore, new studies are expected, with the inclusion of more accurate and reliable data regarding the form of application of the material used in order to determine the exact mechanisms of action and interaction of the placenta

and its derivatives with the body, with appropriate selection of the parameters of mode, time, and quantity of applications of the product used.

CONCLUSION

Human placenta is a nutrient-rich biological material that showed potential to contribute as granulation tissue, reepithelialization and tissue repair of foot ulcers in people with DM, mainly through the use of cryopreserved placental and amniotic membrane allografts, which highlights the importance of considering placenta and its derivatives a useful material for the treatment of difficult-to-heal wounds.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Lima FS, Brandão MGSA, Oliveira DC and Veras VS; **Conception and design:** Lima FS, Brandão MGSA, Oliveira DC and Veras VS; **Data collection, analysis and interpretation:** Lima FS, Brandão MGSA and Oliveira DC; **Writing of the article:** Lima FS, Brandão MGSA, Oliveira DC and Ramalho AO; **Critical revision:** Ramalho AO, Chaves AFL, Araújo TM and Veras VS; **Final approval:** Lima FS, Brandão MGSA, Oliveira DC, Ramalho AO, Chaves AFL, Araújo TM and Veras VS.

AVAILABILITY OF RESEARCH DATA

All data were generated or analyzed in the present study.

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