REVISTA DE LA FACULTAD
DE CIENCIAS DE LA SALUD

Vol. 24(1): 27-40, april - july 2021
i-SSN 0123-7047
e-ISSN 2382-4603

Systematic Review

Cost-effectiveness of nursing interventions for diabetic foot ulcer management: systematic review.

Costo-efectividad de las intervenciones de enfermería para el manejo de úlceras por pie diabético: revisión sistemática.

Custo-efetividade das intervenções de enfermagem para o tratamento das úlceras do pé diabético: uma revisão sistemática.

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ARTICLE INFORMATION:

Article received: January 22, 2020
Article accepted: February 9, 2021
DOI: https://doi.org/10.29375/01237047.3832

Citation. Vásquez-Hernández, S., Rico-Ardila, D., Gómez-Camargo, L., Álvarez-Quintero, L. Cost-effectiveness of nursing interventions for diabetic foot ulcer management: systematic review. MedUNAB. 2021;24(1): 27-40. Doi: https://doi.org/10.29375/01237047.3832

ABSTRACT:

Introduction. Nursing interventions used for the treatment of diabetic foot ulcers include traditional and advanced healing techniques. Often their choice depends on the nurse's personal judgment, rather than recognition of cost-effectiveness.

The objective of this study is to identify the most cost-effective nursing interventions for the management of patients with diabetic foot ulcers. **Methodology.** A systematic review was conducted at Pubmed, Cochrane and the Virtual Health Library. Randomized and non-randomized studies of any nursing intervention used for diabetic foot ulcer management with reported cost-effectiveness were included. The selection of eligible articles was made by two independent reviewers. The risk of bias was assessed using the following guidelines: Critical Appraisal Skills Programme. **Results.** Six of the eight included articles were classified at high risk of bias. The two interventions in which a better cost-effectiveness ratio was evidenced compared to the control group were the use of Beta-Glucan gel (compared to placebo) and negative pressure wound therapy (compared to advanced wet wound therapy). **Discussion.** National and international guidelines for the nursing management of diabetic foot ulcers propose at least 15 different interventions. However, the limited availability of high-quality cost-effectiveness studies makes selection difficult and generates greater variability in nursing practices. **Conclusion.** Cost-effectiveness studies with direct comparisons of nursing interventions for diabetic foot ulcer management are needed.

Keywords:
Diabetic Foot, Patient care management, Leg ulcers, Efficacy, Cost-benefit analysis.

RESUMEN

Introducción. Las intervenciones de enfermería usadas para el tratamiento de las úlceras por pie diabético incluyen técnicas de cura tradicionales y avanzadas. Frecuentemente su elección depende del criterio personal de la enfermera, en lugar del reconocimiento de la relación costo-efectividad. El objetivo de este estudio es identificar las intervenciones de enfermería de mayor costo-efectividad para el manejo de pacientes con úlceras por pie diabético. **Metodología.** Se realizó una revisión sistemática en Pubmed, Cochrane y la Biblioteca Virtual De La Salud. Se incluyeron estudios aleatorizados y no aleatorizados de cualquier intervención de enfermería usada para el manejo de úlcera por pie diabético con reporte de costo-efectividad. La selección de los artículos elegibles fue realizada por dos evaluadores independientes. El riesgo de sesgos fue evaluado con las guías Critical Appraisal Skills Programme. **Resultados.** Seis de los ocho artículos incluidos fueron clasificados con alto riesgo de sesgos. Las dos intervenciones en las que se evidenció una mejor relación costo-efectividad en comparación con el grupo control fueron el uso de Beta-Glucan gel (comparado con placebo) y la terapia de presión negativa (comparada con terapia de herida húmeda avanzada). **Discusión.** Guías nacionales e internacionales para el manejo de enfermería de úlceras por pie diabético proponen al menos 15 diferentes intervenciones. Sin embargo, la escasa disponibilidad de estudios de alta calidad sobre la relación costo-efectividad dificulta la selección y genera mayor variabilidad en las prácticas de enfermería. **Conclusión.** Es necesario realizar estudios de la relación costo-efectividad con comparaciones directas de las intervenciones de enfermería para el manejo de úlceras por pie diabético.

Palabras clave:
Pie Diabético, Manejo de atención al paciente, Úlcera del pie, Eficacia, Análisis costo-beneficio.

RESUMO

Introdução. As intervenções de enfermagem usadas para tratar úlceras do pé diabético incluem técnicas de cura tradicionais e avançadas. Frequentemente, sua escolha depende do julgamento pessoal da enfermeira, ao invés do reconhecimento da relação custo-efetividade. O objetivo deste estudo é identificar as intervenções de enfermagem com um maior custo-efetividade para o tratamento de pacientes com úlceras de pé diabético. **Metodologia.** Foi realizada uma revisão sistemática no Pubmed, Cochrane e na Biblioteca Virtual em Saúde. Foram incluídos estudos randomizados e não randomizados de qualquer intervenção de enfermagem utilizada para o tratamento de úlceras do pé diabético com relatórios de custo-efetividade. A seleção dos artigos elegíveis foi feita por dois avaliadores independentes. O risco de tendências foi avaliado com as diretrizes do *Critical Appraisal Skills Program*. **Resultados.** Seis dos oito artigos incluídos foram classificados como de alto risco de tendência. As duas intervenções que mostraram uma melhor relação custo-efetividade

DOI: https://doi.org/10.29375/01237047.3832 Vol. 24(1): 27-40, april - july 2021

em comparação com o grupo de controle foram o uso de gel de Beta-Glucan (em comparação com o placebo) e a terapia de pressão negativa (em comparação com a terapia avançada de feridas úmidas). **Discussão.** Diretrizes nacionais e internacionais para o tratamento de enfermagem de úlceras do pé diabético propõem pelo menos 15 intervenções diferentes. No entanto, a disponibilidade limitada de estudos de alta qualidade sobre a relação custo-efetividade torna difícil a seleção e leva a uma maior variabilidade nas práticas de enfermagem. **Conclusão.** São necessários estudos que tratem a relação custo-efetividade com comparações diretas de intervenções de enfermagem para o tratamento de úlceras do pé diabético.

Palavras-chave:
Pé diabético; Manejo do cuidado ao paciente; Úlcera do pé; Eficácia; Análise de custo-benefício.

Introduction

Diabetes *mellitus* is a high impact disease due to complications, disability and associated mortality. According to global burden of disease studies, the worldwide prevalence of diabetes in 2016 was 383,453 per thousand inhabitants (95 % CI = 352,588 to 414,576), which represented an increase of 23.6 % (95 % CI = 20.9 % to 26.5 %) from 2006. Consequently, for the same year, diabetes was the ninth disease that caused the most years lived with disability in the world (1). These changes have also meant an increase in mortality attributable to the disease in recent decades, from being the 28th leading cause of death worldwide in 1990 to number 15 in 2017 (2). In Colombia, the Institute for Health Metrics and Evaluation estimated for 2016 that the prevalence of diabetes was 4.2 % (95 % CI= 3.9 % to 4.7 %) (3). However, the review by Vargas-Uricoechea *et al.* shows that the reports of national and international studies conducted in the country have estimated a variation of this prevalence of between 1.8 to 11.2 %, influenced by differences in the diagnosis, the criteria used and the age range studied (4). In contrast to the global situation, diabetes has generated a greater impact in Colombia, being the fifth disease that generated more years of life lived with disability (1) and the ninth cause of death in the country (2,3) in 2016.

There is a clear association between diabetes and its inadequate control with complications such as major cardiovascular events, retinopathy, peripheral neuropathy, peripheral arterial disease, renal disease and increased mortality (5-11). The diabetic foot is the result of the sustained effect over time of neuropathy and peripheral arterial disease combined with the development of infection (12), and the management of associated ulcers is the main cause of prolonged hospitalization in diabetics, contributing to more than 50 % of non-traumatic lower limb amputations (13-16).

In addition to the clinical burden, diabetes generates a high economic and productive impact for those who suffer from it, with the health care costs of people with this disease being 2 to 3 times higher compared to people without diabetes (16-18). According to the World Health Organization's 2016 report on diabetes, the disease contributed to annual direct expenditures of more than USD 827 billion worldwide, a threefold increase compared to 2003 (19). In Latin America, the total direct cost of this disease was estimated at between USD 45 billion and USD 66 billion for 2015. In Colombia, these costs ranged from USD 2,928 million to USD 5,637 million (20).

The specific costs related to diabetic foot care are also known: in England the annual cost generated by diabetic patients with ulceration and amputation is estimated to be between GBP 837 million and GBP 962 million, equivalent to between USD 1.08 billion and USD 1.25 billion, more than 90 % of these costs related to ulceration care (17). In the United States, about USD 790 million have been reported for ulcer care (21), while in Colombia it is estimated at USD 86 million (22,23).

It has been reported that direct costs for the management of patients with diabetic foot in comparison with diabetic patients who do not present this complication have an increase of between USD 11,710 and USD 16,883 in the United States (24). The average cost for each episode of diabetic foot ulcer in developed countries has been evaluated at around USD 25,600, considering that this cost can rise up to 18 times in the presence of complications (amputation, prolonged hospitalization, superinfection) (25).

The most commonly used nursing interventions for the treatment of diabetic foot ulcers include traditional healing techniques such as saline cleansing and application of basic and natural products (e.g., application of honey or sugar cane dressings, petroleum jelly) and advanced healing techniques such as: debridement (autolytic,

surgical and mechanical), larval therapy, growth factors and treatment with chemicals such as dressings (26-31). However, the effectiveness and costs of some of these interventions are questionable, and in most cases their choice is at the personal discretion of the nurse.

The implications for the health, quality of life and economics of the patient, his or her family and the health care system demand the implementation of the latest, most effective and least costly nursing interventions in the management of patients with diabetic foot ulcers. The last systematic review that attempted to identify these interventions was conducted almost 20 years ago (30), including studies with a high risk of bias and without conclusive results on the cost-effectiveness of management. The objective of this study is to identify the most cost-effective nursing intervention for the management of patients with diabetic foot ulcers most recently reported, through a systematic review of the literature to facilitate nursing decision making.

Methodology

Study design

A systematic literature review was developed taking into account a structured review protocol in the academic exercise of the research courses of the UNAB Nursing program. Clinical trials, clinical practice guidelines, observational studies and systematic reviews reporting any technique used for the management of diabetic foot ulcers, in English and Spanish, were included (these two languages were considered in order to obtain information regarding the applicable costs according to the current context). Articles reporting nonpharmacologic or nonphysical management techniques, articles without cost reporting or cost-effectiveness evaluation, duplicate articles, and articles published before March 1, 2013 were excluded. A 5-year window (articles published between March 1, 2013 and March 1, 2018) was considered to identify the most recent available evidence in line with the stated objective.

Participants

Participants in this review were adults with diabetes-associated foot ulcers, regardless of Wagner grade or extent. Patients with other types of foot ulcers were excluded.

Intervention

Any traditional healing technique such as cleansing with saline solution, application of basic and natural products, as well as any advanced healing technique such as debridement (autolytic, surgical and mechanical), larval therapy, negative pressure wound therapy, growth factors and treatment with chemical, pharmacological or other products were considered as nursing interventions for the management of the diabetic foot. Only studies with a control or comparator group were included (no restrictions for this group).

Outcomes

The ulcer healing rate (proportion of ulcers completely healed at a time point) was considered the primary outcome of effectiveness. The direct costs of the intervention or average costs per patient were also considered as outcomes.

Search strategy

The search for articles was performed in Medline using the term:

> ((Diabetic Foot[Title/Abstract]) AND (Patient Care Management[Title/Abstract] OR treatment[Title/Abstract] OR therapy[Title/Abstract] OR therapeutic[Title/Abstract] OR managing[Title/Abstract] OR healing[Title/Abstract] OR guideline[Title/Abstract] OR Techniques[Title/Abstract])) AND (Efficacy[Title/Abstract] OR Cost Efficiency Analysis[Title/Abstract] OR Cost-Utility[Title/Abstract] OR cost-effectiveness[Title/Abstract] OR cost[Title/Abstract] OR costs[Title/Abstract])).

The search was replicated in The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library) and the Virtual Health Library, translating the search term into Spanish for the latter. These databases were selected to allow the search of English and Latin American content.

The selection of the articles was carried out by two evaluators independently of each other. The title, abstract and keywords of each article were reviewed in duplicate. Disagreements were submitted to a third reviewer for consideration to determine potentially eligible articles. Subsequently, the full text of these articles was

DOI: https://doi.org/10.29375/01237047.3832 Vol. 24(1): 27-40, april - july 2021

reviewed by the same group of reviewers, using a similar methodology to determine their final inclusion.

The most relevant characteristics of each included article were summarized in tables to present the year of publication, type of design, population, eligibility criteria, interventions, duration of follow-up and outcomes of each study.

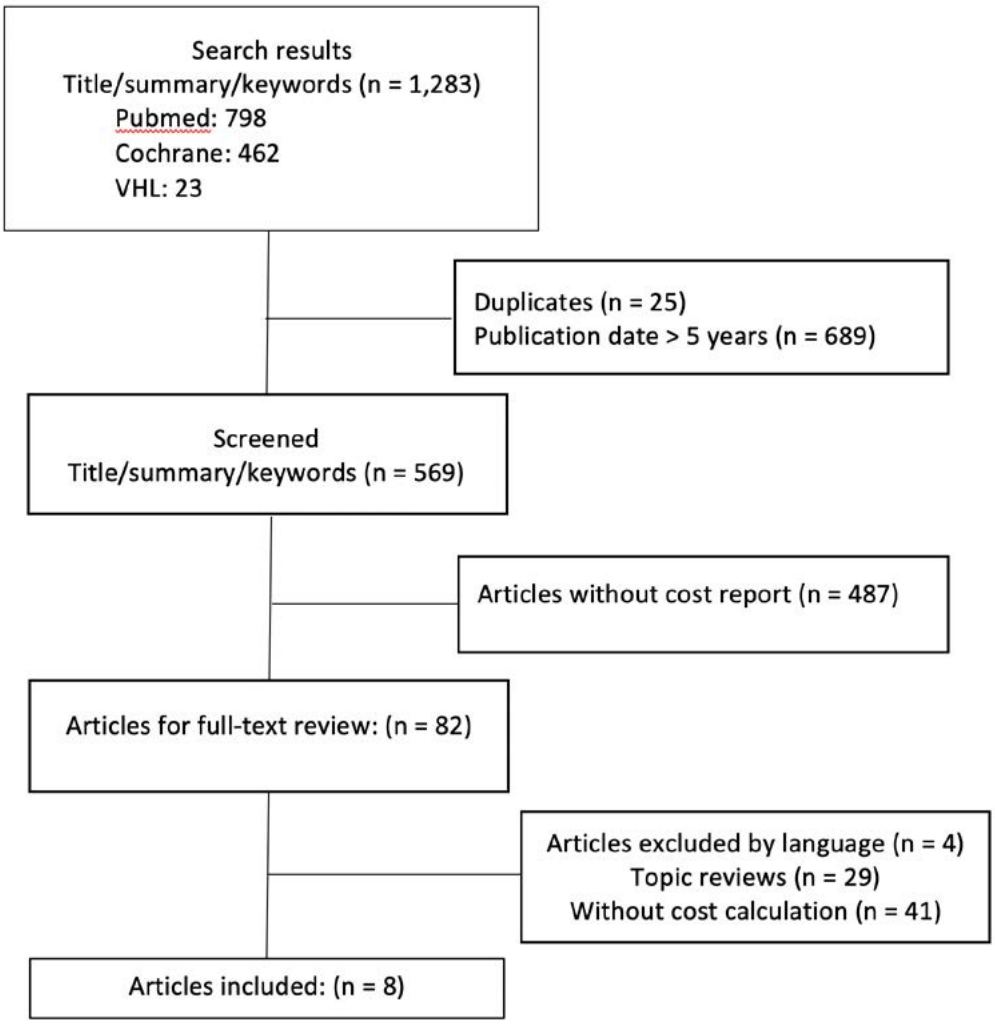
Quality assessment

The methodological quality and risk of bias of the included articles were assessed using the Critical Appraisal Skills Programme (CASP) guidelines according to the design of each study identified. Here again, two reviewers, independently of each other, performed this procedure. Disagreements were discussed and resolved.

Results

Application of the term in the databases showed 1,283 search results. After excluding duplicate articles and articles with publication dates older than 5 years, the title, abstract, and keywords of 569 articles were reviewed to determine their eligibility. From this group, 82 articles were selected for full-text review, leading to the final inclusion of 8 articles that reported cost-effectiveness of techniques for the management of diabetic foot ulcers (32-39). Figure 1 shows the search and selection process for these items.

Figure 1. Article search and selection process.



n: Number, VHL: Virtual Health Library
Source: Own preparation.

Five randomized clinical trials and three retrospective cohort studies were included. Seventy-five percent of these studies were conducted in the United States, so most of the costs were reported in United States dollars. The most relevant characteristics of the articles included are presented in Table 1. Sample sizes ranged from 26 to 24,898 included patients, with average ages ranging from 53 to 75 years. In all studies, the highest percentage of the sample corresponded to men (53 %-75 %) and follow-up times were between 20 weeks and one year.

Table 1. Characteristics of studies included

Autor, año	Location	Design	Number of patients	Age, years, mean (SD)	Men n (%)	Monitoring duration in weeks
Cutting, 2017 (32)	Russia	Randomized clinical trial	54	60.8; IQR = 24.4 - 87.9	24 (40)	12
Driver, 2014 (33)	United States	Randomized clinical trial	324	58.5 (12)	256 (79)	40
Waycaster, 2016 (34)	United States	Randomized clinical trial	475	58.9 (11.4)	338 (71.2)	20
Zelen CM, 2017 (35)	United States	Randomized clinical trial	40	61.5(10.9)	28 (70)	12
Gilligan, 2015 (36)	United States	Randomized clinical trial	26	62.2 (12.2)	18 (69.2)	12
Gilligan, 2015 (37)	United States	Retrospective cohort	24,898	63.6 (14)	13,569 (54.5)	20
Rice, 2015 (38)	United States	Retrospective cohort	21,122	76.3 (7.5)	9,853 (46.6)	81
Wilarusmee, 2014 (39)	Thailand	Retrospective cohort	111	53.4 (11.4)	61 (54.9)	50

SD: Standard deviation, IQR: Interquartile range
Source: Prepared by author.

Table 2 shows the eligibility criteria, interventions and outcomes for each study. The interventions/exhibitions assessed were: Beta-Glucan gel, negative pressure wound therapy, Becaplermin gel, open structure matrix with human reticular acellular dermis plus standard care, pork-derived extracellular wound matrix, bioengineered living cell construct or human fibroblast-derived

Table 2. Eligibility criteria, interventions and outcomes of each study.

Author, year	Inclusion criteria	Exclusion criteria	Intervention/ exhibition	Comparator	Outcomes
Cutting, 2017	• Age ≥ 18 years. • Diabetes mellitus type 1 o type 2. • Wagner ulcer grade 1 or grade 2 skin thickness, not including tendon, joints or bone. • Localized ulcer on foot or lower leg present at least 4 weeks, but less than 2 years. • Adequate blood supply determined as the presence of palpable pulse in the corresponding foot. • Area of ulcer > 1 cm^2	• Ankle-brachial index <0.7 • Malnutrition • Clinical evidence of gangrene at any site or active or extensive cellulitis. • Medical complications that make the patient an unsuitable candidate for the study (e.g., diabetic nephropathy). • Active osteomyelitis. • Necrotic toes on the foot where the study ulcer is located. • Surgical procedure three weeks prior to inclusion other than debridement of the ulcer. • Random blood glucose > 450 mg / dl	Beta-glucan gel	Placebo	• Cure rate • Average number of weeks in cured state. • Average cost per patient • Incremental cost per additional week cured.

DOI: https://doi.org/10.29375/01237047.3832 Vol. 24(1): 27-40, april - july 2021

Driver, 2014	• Age ≥ 18 years. • Diabetes mellitus type 1 o type 2. • Wagner ulcer grade 2 or grade 3 at plantar, dorsal or calcaneus level ≥ 2 cm area after debridement. • Adequate perfusion	• Acute Charcot recognized • Ulcers due to electrification, chemical or radiation burns and those due to collagen vascular disease, malignant neoplasm, untreated osteomyelitis, or cellulitis. • Uncontrolled hyperglycemia (HgG 12%). • Inadequate perfusion of the limb. • Treatment with drugs such as corticosteroids, immunosuppressants, chemotherapy, growth factor products; in the 30 days prior to the start of the study.	Negative pressure wound therapy	Advanced wet wound therapy	• Cure rate • Direct cost of therapy. • Cost per cm^2 reduced on the wound surface.
Waycaster, 2016	• Age ≥ 19 years. • Diabetes mellitus type 1 o type 2. • Ulcers with area > 1 cm2 and < 40 cm^2.	• Inadequate perfusion of the limb. • Treatment with drugs such as corticosteroids, immunosuppressants, chemotherapy, growth factor products; in the 30 days prior to the start of the study.	Becaplermin gel	Placebo/ standard care	• Cure rate • Direct cost of therapy • Cost per cm^2 reduced on the wound surface.
Zelen, 2017	• Age ≥ 18 years • Diabetics with at least one neuropathic foot ulcer. • Area of ulcer > 1 cm^2 • Failure of conservative treatment of at least 4 weeks. • Adequate renal function. • Adequate circulation of the limb. • Ulcer without signs of infections. • Serum creatinine <3 mg/dl • HbA1c < 12 %.	• Wagner ulcer grade 3. • Area of ulcer > 25 cm^2 • HbA1c > 12 % over the last 90 days. • Known history of poor adherence to medical treatments. • Treatment with radiotherapy or chemotherapy. • Local cutaneous neoplasia, autoimmune diseases.	Open structure matrix with human reticular acellular dermis + standard care	Standard care	• Cure rate • Direct cost of therapy
Gilligan, 2015	• Age ≥ 18 years. • Diabetes mellitus type 1 o type 2. • Ulcers extending through the epidermis and dermis, but without exposed tendon or bone. • Chronic diabetic ulcer with granulation tissue. • Size of the ulcer ≥1 cm^2 and ≤ 16 cm^2 • Wound present over 4 weeks.	• Malnutrition • Known allergy to pork products, dextran, EDTA or gelatin. • Known hypersensitivity to the components of the intervention product. • Severe arterial disease (ankle-brachial index < 0.65). • History of radiotherapy at the ulcer site. • Treatment with corticosteroids or immunosuppressants. • Vasculitis, severe rheumatoid arthritis or other collagen vascular disease. • Erythema or purulence associated with severe wound site infection. • Signs and symptoms of cellulitis, osteomyelitis or avascular necrosis. • Perform hemodialysis. • Poor blood supply to ulcers.	Pork-derived extracellular wound matrix	Human fibroblast-derived dermal substitute	• Cure rate • Time with the wound closed. • Average cost per patient
Gilligan, 2015	• Patients with superficial diabetic plantar ulcer. • Adequate lower extremity arterial perfusion for wound healing.	NR	Becaplermin gel	Standard care	• Cure rate • Weeks with the wound closed. • Risk of amputation • Direct cost of therapy.

Rice, 2015	• Age ≥ 65 years. • Diabetes mellitus • Patients with at least two separate claims with a diagnosis of diabetes and at least one claim with a diagnosis of foot ulcer.	NR	Bioengineered living skin cell construction or human fibroblast-derived dermal substitute	Standard care	• Lower limb amputation rate. • Average cost per patient
Wilarus-mee, 2014	• Diabetes mellitus • Presence of a single foot wound. • Ability to walk without • assistive device • Availability of data for at least six months of follow up. • No presence of gangrenous wounds, necrotizing fasciitis, abscesses, or osteomyelitis.	NR	Larval therapy	Standard care	• Cure rate • Incidence of wound healing. • Direct cost of therapy.

NR= Not reported

Source: Prepared by author.

dermal substitute, and larval therapy. The most frequent comparison groups were treated with standard care (SC) or placebo.

a) Beta-glucan gel

Cutting *et al.* performed an economic simulation model extrapolating data from a randomized clinical trial comparing Beta-Glucan gel with placebo for the treatment of diabetic foot ulcers. In the clinical trial, no significant differences were observed between the groups in relation to cure rate and average time to complete cure. However, the group receiving Beta-Glucan had a higher incidence of ulcer healing at week 8 of treatment compared to the placebo group (44 % versus 17 %, P = 0.03) (32).

The average treatment cost was GBP 1,459 (approximately USD 1,886) for the Beta-Glucan gel-treated group and GBP 1,358 (approximately USD 1,756) for the placebo group at the 12-week follow-up. According to the simulation model for a one-year period, Beta-Glucan would be expected to have a 94 % healing rate of ulcers, while the healing rate of the placebo group would be 78 %, allowing an annual savings of GBP 503 per patient (about USD 650) (32).

Negative pressure wound therapy and advanced wet wound therapy

A retrospective post hoc economic cost analysis of the treatment of 324 patients with diabetic foot ulcers included in a multicenter clinical trial in which they were randomized to receive either negative pressure wound therapy (NPWT) or advanced wet wound therapy (AHWT) was developed by Driver *et al.* In this study, 43.2 % of patients in the NPWT group achieved complete ulcer closure compared to 28.9 % in the AHWT group (p = 0.007). In the NPWT group, the average cost to achieve the cure rate was USD 10,172 compared to USD 9,505 in the AHWT group, while the average cost per square centimeter (cm^2) of closure was USD 1,227 in the NPWT group and USD 1,695 in the AHWT group. (33)

b) Becaplermin gel

Two articles reported Becaplermin gel (BCP) treatment as an intervention; in both cases the data were extrapolated from randomized clinical trials in which the intervention was always superior to the comparator (placebo or standard care in diabetic foot ulcers) in relation to healing rate (34, 36).

The first used data from 475 patients included in three randomized clinical trials in which the use of BCP was compared with placebo or SC, to develop a one-year prediction model. According to this model, it was observed that at week 20 the percentage of patients with complete wound closure in the BCP group was 50 % versus 35 % in the placebo group (p = 0.015). The placebo group model showed a higher estimated cost to achieve ulcer closure in the totality of patients compared to those operated with BCP (USD 6,809 versus USD 4,414), as well as a higher cost per cm^2 of ulcer (USD 3,501 versus USD 2,006) (34).

The results were similar in the second article, which used data from a retrospective cohort study in which 24,898 patients with diabetic foot ulcers who received BCP or

DOI: https://doi.org/10.29375/01237047.3832 Vol. 24(1): 27-40, april - july 2021

SC and were followed for 20 weeks between 1998 and 2004, to determine the number of weeks with the wound closed, the rate of healing, the risk of amputation, and the direct costs of each therapy. The BCP group had a higher cure rate compared to the SC group (33.5 % versus 25.8 %, respectively; $p < 0.0001$) and a decreased risk of amputation (4.9 % versus 6.4 %, respectively; $p < 0.0001$). After developing a one-year prediction model, it was estimated that the duration of time with the wound closed in the BCP group was longer compared to the SC group (16.1 versus 12.5 weeks, respectively). The 48.1 % of patients with BCP had healthy wounds at 1 year versus 38.3 % in the SC group, and the risk of amputation was lower in the BCP group (6.8 % versus 9.8 %). Finally, the estimated annual costs to achieve ulcer healing were USD 21,920 for BCP and USD 24,640 for SC (36).

c) Pork-derived extracellular wound matrix

A clinical trial randomized 26 patients with diabetic foot ulcers in a 1:1 ratio to receive treatment with porcine-derived extracellular wound matrix (PDEWM) or a human fibroblast-derived dermal substitute (HFDS) with a 12-week follow-up period to determine healing rate and time with wound closure. No significant differences in healing rates or time with wound closure were observed between both groups. Average costs per patient were estimated using an economic simulation model with one-week cycles. The estimated cost for ulcer healing over 12 weeks was USD 2,522 for the PDEWM-treated group compared with USD 3,889 for the HFDS-treated group. (37)

d) Larval therapy

Wilarusmee *et al.* compared larval therapy (LT) with standard care in 111 patients with diabetic foot ulcers from a retrospective cohort from Thailand. In this study, the estimated incidence of wound healing was 5.7 / 100 patients (95 % CI= 4.49 to 7.32) and the mean healing time was 14 weeks for the larvae-treated group. Ulcer healing was 7.87 times higher in the LT versus SC group ($p < 0.001$). The median cost in the LT group was USD 292.82 while that of SC was USD 490 (39).

e) Other interventions

Two articles compared other interventions with standard care. The first, a randomized clinical trial in 40 patients with 1:1 allocation to receive open-label treatment with human acellular reticular dermis plus standard care or standard care alone (35), and the second a retrospective cohort in which 21,122 patients were included to compare patients who received a bioengineered living skin cell construction or human fibroblast-derived dermal substitute with patients who received standard care (38). In both articles, the results were superior in terms of effectiveness (cure rate) and average cost per patient in the intervened groups.

Assessment of the methodological quality of the articles

In general, the methodological quality of the included articles was low: six of the eight studies were classified with a high risk of bias. Potential selection and reporting biases were present in more than half of the studies, while the possibility of relevant confounding biases was evident in only one randomized study. The results of the assessment are presented in Table 3 and Table 4. The quality of the studies makes it only possible to consider the results of Cutting *et al.* (32), and Driver et al (33), whose interventions relate to the use of Beta-Glucan

Table 3. Methodological quality of the clinical trials included.

Author, year	Random assignment/ concealed randomization sequence	Adequate blinding*	Infrequent loss to follow-up**	Free of evidence of co-interventions	Homogeneous groups at the beginning of the study	Analysis by intention to treat	Industry-sponsored	Risk of bias in general
Cutting, 2017	Probably yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Driver, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Waycaster, 2016	Probably yes	Yes	NR	Probably no	Yes	No	Yes	High
Zelen, 2017	Yes	No	Yes	Probably no	No	Yes	No	High
Gilligan, 2015	Yes	No	NR	Probably no	Yes	NR	NR	High

*Blinding of patients and clinicians.
** Defined as less than 15 % of randomized patients.
NR= Not reported.
Source: Prepared by author.

Table 4. Methodological quality of the cohort studies included.

Author, year	Adequate recruitment	Appropriately measured exposure	Adequately measured outcomes	Blind awarding of outcomes	Adjusted for confounding factors	Infrequent loss to follow-up*	Industry-sponsored	Risk of bias in general
Gilligan, 2015	Probably yes	Probably yes	Probably yes	NR	Yes	Yes	No	High
Rice, 2015	Probably yes	Probably yes	Probably yes	NR	Yes	Yes	Yes	High
Wilarusmee, 2014	Probably yes	Probably yes	Probably yes	NR	Yes	Yes	No	High

** Defined as less than 15 % of randomized patients
NR = Not reported
Source: Prepared by author.

compared to placebo, and negative pressure wound therapy compared to advanced wet wound therapy, respectively.

Discussion

This is the second systematic review conducted after approximately two decades, with the aim of identifying the nursing interventions for the management of patients with diabetic foot ulcers with the best cost-effectiveness ratio.

Although in the first systematic review only randomized clinical trials were eligible, this one had a broader approach as it not only included articles of interventions for ulcer treatment but also articles reporting interventions for ulcer prevention such as: podiatry, screening and prevention programs, footwear, education for the use of compression and elastic stockings. Despite this, the results were very similar to the review here, although there is a very diverse report on interventions for the management of diabetic foot ulcers. Most articles lack methodological rigor, and therefore have a high risk of bias, maintaining uncertainty about the best treatment option in terms of effectiveness. Additionally, this review found only one article that incorporated both efficacy and cost outcomes related to treatment (skin replacement) (30).

In the care of patients with diabetic foot, nurses with different roles can intervene according to their academic background and expertise; from the general nurse, whose activities are focused on the prevention of complications through educational interventions, to the nurse specialist in wound management or diabetes, whose interventions are focused on complementing the treatment of ulcers through different healing techniques (40).

Various nursing or multidisciplinary practice guidelines establish that the management of diabetic foot ulcers should be individualized and the selection of interventions or techniques will depend on the conditions of the ulcer such as: vascular perfusion, presence of infection, bone or structural deformities, type of footwear and pressure sensitivity problems (41-46). However, these assessment criteria are subjective, and in addition, the guidelines propose at least 15 different techniques for the management of these ulcers, putting at risk the reproducibility of intervention selection among nursing professionals and the outcomes of patients with this condition. On the other hand, efficacy in most of the proposed interventions has been evaluated in comparison with standard care or placebo, so superiority among these interventions remains unevaluated.

Additionally, economic evaluation studies of these interventions are scarce. With regard to traditional healing techniques, no article evaluating costs was found in the current review. In contrast, in advanced healing techniques, eight studies were found that included this evaluation. However, it is only possible to consider the results of the randomized clinical trials of Cutting, *et al.* (32), and Driver, *et al.* (33) due to the high risk of bias in the other studies. The results of Cutting, *et al.* (32) suggest that management with Beta-Glucan is superior to no management, as it increases healing rates and reduces costs in patients with diabetic foot ulcers. However, by having a placebo group as a comparator, this study is not very pragmatically oriented, and does not answer the question of superiority in terms of cost-effectiveness when compared to other nursing interventions, and is far from a possible application in real clinical practice. In addition, this product is not marketed in Latin America, so its implementation would be extremely limited.

Driver, *et al.*'s studies (33) compared two techniques commonly used in Latin America: negative pressure wound therapy and advanced wet wound therapy. According to the results, nursing interventions for the management of diabetic foot ulcers should lean toward

DOI: https://doi.org/10.29375/01237047.3832 Vol. 24(1): 27-40, april - july 2021

the use of negative pressure wound therapy rather than advanced wet wound therapy for more cost-effective outcomes. However, it should be noted that these findings are limited to patients older than 18 years, with Wagner ulcer grade 2 or grade 3 at plantar, dorsal or calcaneus level ≥ 2 cm in area after debridement and adequate perfusion, and who also do not have any of the characteristics that were taken into account as exclusion criteria in this study (e.g. uncontrolled hyperglycemia[Glycosylated hemoglobin > 12%]; treatment with drugs such as corticosteroids, immunosuppressants, chemotherapy or growth factor products in the last 30 days). Considering that this study (Driver *et al.*) was developed in the United States, the costs of this intervention (average cost per cm2 of closure USD 1,227 for negative pressure wound therapy) could vary in Latin America.

The current systematic review has some limitations. First, the search for information was restricted to the databases mentioned in the methodology and did not include other types of literature sources not published in indexed databases (such as results presented at events or scientific associations). The search and selection of articles was performed entirely by the authors without the support of a librarian or information professional, so additional information may not have been incorporated.

Second, the search was restricted to articles published in the last five years, which may have influenced the number of eligible studies. However, this search was aimed to identify the most recent evidence available, so manuscripts published in this period can be considered as the most current evidence. Moreover, their results were not very different from those found in the previous systematic review on this topic, which reflects the fact that the economic evaluation of these interventions is an area in which insufficient progress has been made.

Third, most of the economic evaluations of the included articles were developed in post hoc studies using predictive models, so their accuracy may be inadequate. Since the two articles with adequate methodological quality were developed in Russia and the United States, it is difficult to extrapolate their results to countries with different sociodemographic and economic indexes, such as Colombia or other Latin American countries.

Finally, the small number of primary studies included, their heterogeneity, as well as their methodological shortcomings prevent conclusions from being drawn. The applicability of the findings of this review is compromised due to the unavailability of one of the interventions in the region, but above all due to the lack of direct comparisons between these interventions.

Conclusions

The available evidence remains very limited and of low quality to identify the most cost-effective nursing intervention for the management of diabetic foot ulcers. Pragmatic randomized clinical trials with adequate sample sizes, methodological rigor, with direct comparisons of these interventions, and accompanied by economic evaluations are required to objectively guide nursing care in patients with this condition.

Conflicts of Interest

The authors of this article declare that there is no conflict of interest.

Sources of funding

This project did not obtain any sources of external funding. Its development derives from the authors' own resources.

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