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REVIEW

Regenerative medicine in the care of diabetic foot ulcers. A Systematic Review

Medicina regenerativa en el cuidado de las úlceras del pie diabético. Una Revisión Sistemática

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ABSTRACT

Introduction: The pluripotency of stem cells (SC) and platelet-rich plasma (PRP) makes them potential candidates to accelerate tissue repair processes in lesions such as diabetic foot ulcers (DFU).
Objective: Our objective was to evaluate the current evidence on the benefits of healing DFUs that do not respond to conventional treatment with SC and/or PRP.

Method: Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we systematically review original studies published in the last 5 years and indexed in Web of Science, Scopus, CUIDEN, and PubMed to evaluate the effects of SC and/or PRP on skin markers, healing time and adverse effects in DFU. The study was registered in PROSPERO (CRD 42024537847).
Results: Among 107 records identified in the search, 5 studies met the inclusion criteria. DFUs treated with topically administered PRP or intralesional injection achieved a significant ($p < 0.05$) reduction in ulcer/ wound area. The overall cure rate improved significantly ($p < 0.05$) after the application of SC. Treatment with SC was able to reduce the amputation rate non-significantly ($p > 0.05$). The epithelialization or healing processes did not experience significant changes ($p > 0.05$) after the use of PRP or SC. No serious adverse effects were reported.
Conclusion: Cell therapy with SC and/or PRP on DFUs that do not heal with conventional treatment is a safe and effective therapeutic option.

Keywords: Diabetes Mellitus; Diabetic Foot Ulcers; Regenerative Medicine, Platelet Rich Plasma; Stem Cells.

RESUMEN
Introducción: La pluripotencialidad de las células madre (CM) y del plasma rico en plaquetas (PRP) los convierte en posibles candidatos para acelerar los procesos de reparación tisular de lesiones como las úlceras del pie diabético (UPD).
Objetivo: Nuestro objetivo fue evaluar la evidencia actual sobre los beneficios de la terapia con CM y/o PRP de las UPD que no responden a tratamiento convencional.
Método: Con base a las *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA), revisamos sistemáticamente estudios originales publicados en los últimos 5 años e indexados en Web of Science, Scopus, CUIDEN y PubMed para evaluar los efectos de las CM y/o PRP sobre los marcadores cutáneos, tiempo de cicatrización y efectos adversos en UPD. El estudio fue registrado en PROSPERO (#CRD 42024537847).
Resultados: Entre 107 registros identificados en la búsqueda, 5 estudios cumplieron los criterios de inclusión. Las UPD tratadas con PRP administrado tópicamente o mediante inyección intralesional consiguieron una reducción significativa ($p < 0,05$) del área de la úlcera/herida. La tasa global de curación mejoró significativamente ($p < 0,05$) tras la aplicación de CM. El tratamiento con CM fue capaz de reducir de forma no significativa ($p > 0.05$) la tasa de amputación. Los procesos de epitelización o cicatrización no experimentaron cambios significativos ($p > 0,05$) tras el uso de PRP o CM. No se reportaron efectos adversos graves.
Conclusiones: La terapia celular con CM y/o PRP sobre las UPD que no cicatrizan con tratamiento convencional es una opción terapéutica segura y eficaz.

Palabras Clave: Diabetes Mellitus; Úlceras del Pie Diabético; Medicina Regenerativa, Plasma Rico en Plaquetas; Células Madre.

INTRODUCTION

Diabetes *mellitus* (DM) is a chronic metabolic disorder characterized by hyperglycemia because of insufficient insulin production or endogenous resistance to its action [(1)]. The World Health Organization (WHO) considers it a serious global public health problem because it is the most common endocrinological disorder [(2)]. The International Diabetes Federation (IDF) estimates that 500 million people have DM and estimates that by 2040 this figure will even increase to 800 million [(3)]. 10.6% of the world's adult population suffers from glucose intolerance, which places them at high risk of developing type 2 diabetes; in Spain the prevalence of diabetes is 14.8%, being the second highest rate in Europe. Healthcare expenditure related to DM in Spain is around 15.5 billion dollars, placing it among the group of 10 countries with the highest healthcare expenditure on this disease [(4)]. DM can present both acute and chronic complications, the latter including diabetic foot ulcers (DFU) whose etiopathogenesis is multifactorial, with neuropathy, trauma, secondary infection and vasculopathy as the main factors involved [(5)].

DFUs are the main cause of non-traumatic amputations and one of the most disabling complications for patients with DM [6]. Risk factors such as age, duration of DM, smoking, obesity, hypertension, low ankle-brachial index (ABI) or high neutrophil/lymphocyte ratio (NLR) closely related to the appearance of DFUs [7] and determine their severity. It is estimated that approximately 16% of diabetics will suffer from DFU during their lifetime, and that around 85% of them would have been potentially avoidable [8].

It is estimated that a lower limb amputation is performed every 30 seconds somewhere in the world because of DM. Failed conventional treatments can result in up to 20% of these amputations, thus increasing morbidity and deteriorating the patient's quality of life [9].

The healing capacity of diabetic patients is conditioned by the disruption of angiogenic mechanisms [10], the increase in inflammatory processes and the alteration of tissue remodeling by the decrease in the synthesis and release of growth factors [11]. In addition, hyperglycemic states increase oxidative stress, which negatively affects wound healing [12]. The aforementioned factors alter one or more of the stages of healing, thus preventing complete repair of damaged tissue even when appropriate care and treatment have been provided [13]. For this reason, innovative therapeutic interventions are being sought to treat DFUs that do not respond to conventional treatment and thus avoid, as far as possible, their most serious consequences, since they represent a problem of quality of life for patients and an economic challenge for health systems [14]. In this sense, regenerative medicine covers a new emerging area of medical sciences that involves the functional restoration of tissues or organs caused by serious injuries or chronic diseases. Currently, there are two competing technologies that can repair and restore damaged tissues: platelet-rich plasma (PRP) -based therapies and stem cell (SC)-based therapies [15].

Topical administration of growth factors through PRP or SC therapy in the treatment of DFUs is considered as complementary or rescue when the conventional approach has failed [16]. Cell therapy, used as a biological dressing in the management of chronic vascular ulcers in lower extremities that are resistant to other treatments, has shown promise [17]. It allows tissue repair after transplantation of SC populations that have the capacity to self-renew and give rise to several types of functional mature cells called "tissue regeneration units" [18]. The pluripotency of SCs makes them potential candidates for tissue repair thanks to the secretion of cytokines, chemokines and growth factors [19]. Mesenchymal stem cells (MSCs) used in the treatment of DFUs are the most used and include bone marrow-derived mononuclear cells (BM-MNCs), bone marrow CD34 $^{+}$ cells, and bone marrow-derived mesenchymal stem cells (BM-MSCs) [20]. These cells promote angiogenesis in the transplant bed by increasing blood flow in the treated area [21].

Regenerative medicine therapy based on PRP, a portion of plasma with a higher than baseline platelet concentration, has been successfully used to accelerate tissue regeneration processes in areas such as traumatology [22], otorhinolaryngology [23], sports medicine [24], plastic surgery [25], vascular surgery [26] and dermatology [27], among others. The efficacy of PRP treatment in the healing of chronic wounds has been described, with the release of 95% of growth factors observed in the first hour after application [28–30].

Due to their purported ability to accelerate the healing process, regenerative medicine employing SC [31–33] and PRP [30–32] has gained widespread use in the field of chronic wound repair as superior to standard of care or conventional treatment. SC and PRP are gaining worldwide attention as conventional treatments yield inadequate results and DFUs remain prevalent in the aging population. Therefore, this review aims to analyze clinical trials evaluating the efficacy of PRP and/or autologous BM-MSC or BM-NMSC therapy in contrast to conventional methods, administered intralesional or topically, in the treatment of DFUs in patients with poorly progressing DM who are unresponsive to conventional treatment.

MATERIAL AND METHOD

Study design and search strategy

The current protocol was registered in the database (International Prospective Register of Systematic Reviews (PROSPERO) (#CRD 42024504290). The *Preferred Statement was used to conduct systematic review. Reporting Items for Systematic Reviews and Meta- Analysis* (PRISMA) [34]. Clinical trials were retrieved from the electronic databases Medline (PubMed), Scopus, Web of Science (WOS) and the bibliographic database of the Index Foundation for Nursing Care (CUIDEN) from November 2023 to May 2024. Publications from the last 5 years were included, given the novelty of regenerative medicine treatments in DFUs. The search terms included Health Sciences Descriptors (DeCS) [35] and *Medical Subject Headings* (MesH) [36] plus free words related to UPD and cell therapy: *ulcer, diabetic foot ulcer* (diabetic foot ulcer*), bone marrow* (bone marrow), *stem cells* (stem cells), *platelet-rich plasma, wound healing*, *skin regeneration*. The Boolean operators AND and OR were used to connect the terms. The search sequences used are detailed in Table 1.

Table 1: Search sequences.

Database	Keywords	Number of studies
Medline (PubMed)	("diabetic foot ulcer"[Title/Abstract] OR "diabetic foot"[Title/Abstract] OR "foot ulcers disease"[Title/Abstract]) AND ("cell therapy"[Title/Abstract] OR "cell treatment"[Title/Abstract] OR "stem cell therapy"[Title/Abstract] OR "stem cell treatment"[Title/Abstract] OR "platelet rich plasma treatment"[Title/Abstract] OR "platelet rich plasma therapy"[Title/Abstract]) AND ("cure" OR "heal" OR " scarring " [Title/Abstract]). Filters: Full text, Trial, in the last 5 years	52
Scopus	("diabetic foot ulcer"[Title/Abstract] OR "diabetic foot"[Title/Abstract] OR "foot ulcers disease"[Title/Abstract]) AND ("cell therapy"[Title/Abstract] OR "cell treatment"[Title/Abstract] OR "stem cell therapy"[Title/Abstract] OR "stem cell treatment"[Title/Abstract] OR "platelet rich plasma treatment"[Title/Abstract] OR "platelet rich plasma therapy"[Title/Abstract]) AND ("cure" OR "heal" OR " scarring "[Title/Abstract]). in Title Abstract Keyword in All Text - with Publication Year from 2019 to 2024. Filters: Full text, Trial, in the last 5 years	17

Database	Keywords	Number of studies
Web Science (WOS)	of((diabetic foot ulcer OR diabetic foot OR foot ulcers disease) (topic)) AND ((cell therapy OR cell treatment OR platelet rich plasma treatment OR platelet-rich plasma therapy) (Topic)) AND (cure OR heal OR scarring) (Topic)) anywhere Publication 2019-2024, Filters: Full text, Trial, in the last 5 years	24
TAKE CARE	diabetic foot ulcer AND cell therapy, platelet-rich plasma therapy, AND cure, scarring)	14

The search results were downloaded to a personal database, filtered, extracted, analyzed, and synthesized to obtain qualitative and quantitative data. The data collection procedure for this study was carried out following the PRISMA flowchart [34]. This included identifying relevant studies in the databases, searching for duplicates, titles and abstracts, assessing the full text for eligibility, and extracting and analyzing the included studies.

Eligibility criteria

Studies were selected according to the inclusion and exclusion criteria. Inclusion criteria were established according to the PICOS framework [37], including:

P (Population): adult patients diagnosed with type 1 DM and type 2 DM presenting with difficult-to-heal DFUs requiring complex care, who are not infected and/or without osteomyelitis, and who do not respond to conventional treatment; I (Intervention): Biological cell therapy or therapy based on: PRP, BM-MSCs or BM-MNCs; C (Comparison): same conditions with placebo, conventional therapy, sham therapy or no intervention or pre/post comparison data group; O (Outcome): cutaneous markers (area, volume, epithelialization/scarring, amputation), healing time (total time to closure of the DFU) and adverse effects (AE) of the treatment; S (Study) : clinical trial.

Exclusion criteria were studies using BM-MSCs, BM-MNCs, or PRP for treatment other than DFUs, animal studies, bibliographic, systematic, meta-analyses, and/or editorial reviews, and articles published before 2019. In addition, EndNote X9 software (Clarivate, Philadelphia, PA, USA) was used to remove duplicate studies. Subsequently, three independent reviewers screened the titles and abstracts of the studies according to accessibility criteria. Any discrepancies between reviewers were resolved through discussion to reach a consensus.

Evaluation of Methodological Quality

The Critical Review Form for Quantitative Studies developed by the Occupational Therapy Evidence-Based Practice Research Group at McMaster University (McMaster) was used [38].

Data extraction

Data were manually collected and assessed from studies that met the inclusion criteria and entered the extraction spreadsheet. Data recorded in the extraction included

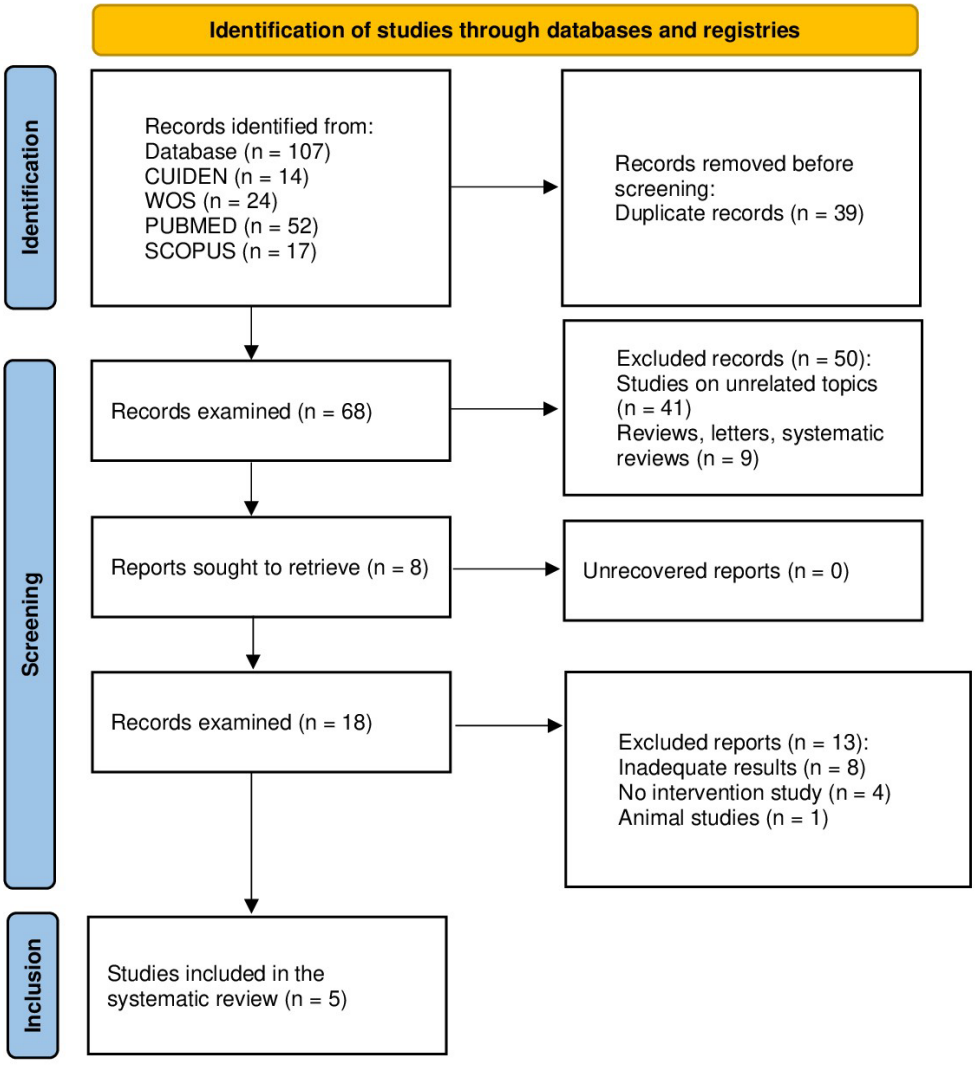
author(s), year, date of publication and country, participant status, study design, intervention method and outcomes, and finally the conclusions of each trial.

RESULTS

Selection of studies

A comprehensive search of multiple databases resulted in the identification of a substantial number of studies. Specifically, the initial search yielded 107 records from various sources, including Medline (PubMed) (n = 52), WOS (n = 24), Scopus (n = 17), and CUIDEN (n = 14). Of these, 39 records were removed due to duplications, leaving 68 records for screening. Upon further evaluation, 50 records were removed, leaving 18 studies for full-text assessment, of which 13 records were eliminated due to inadequate results (n = 8), non-interventional studies (n = 4), or studies performed on animals (n = 1). Ultimately, 5 studies [39–43] met the inclusion criteria and were included in the present systematic review (Figure 1).

Figure 1: Flowchart depicting the processes of identification and selection of relevant studies according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [34].



Methodological quality assessment

McMaster form [38] obtained scores between 12 and 14 points, representing a minimum quality of 75% and a maximum quality of 87.5% (Table 1). Of the 5 studies [39–43] included 3 studies [39–41] achieved "very good" quality and 2 studies [42,43] "good". No articles were excluded for not reaching the minimum quality threshold (Table 2).

Table 2: Assessment of methodological quality according to quantitative studies developed by the Occupational Therapy Evidence-Based Practice Research Group at McMaster University [38].

Study and year	Items																T	%	MQ
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
Askø et al. [26] 2022	1	1	0	0	1	1	1	1	1	1	0	0	1	1	1	1	12	75	G
Torre et al. [24] 2020	1	1	0	1	1	1	1	1	1	1	0	0	1	0	1	1	12	75	G
Lu D., et al. [27] 2019	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	14	87.5	VG
Orellano et al. [23] 2021	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	14	87.5	VG
Smith et al [25] 2020	1	1	1	1	1	1	1	1	1	1	0	1	0	1	0	1	13	81.25	VG

Abbreviations: (T) total items met, (1) Criterion met, (0) Criterion not met, (MQ) methodological quality, (G) good, (VG) very good, (item 1) clear statement of the purpose of the study, (item 2) relevant literature, (item 3) adequacy of the study design, (item 4) detailed description of the sample, (item 5) justification of the sample size, (item 6) sample size, (item 7) ethics and consent, (item 8) detailed description of the intervention, (item 9) contamination, (item 10) co -intervention , (item 11) statistically significant results, (item 12) appropriate methods of analysis, (item 13) clinical significance, (item 14) dropouts, (item 15) appropriate conclusions, (item 16) biases.

Characteristics of the included studies

The included investigations (Table 3) were carried out between 2019 and 2022. This study included 2 randomized controlled trials [39,41], and 3 prospective studies [40,42,43]. The studies were conducted in Denmark [43], Spain [42], China [41], Uruguay [40] and the United Kingdom [39]. The total number of DFU patients included in the studies at baseline was 71 participants. All were over 18 years of age diagnosed with DM 1 [39,40,42,43] or DM 2 [39–43] according to the WHO DM Diagnostic Standard [2] and with at least one DFU per lower limb. Three studies with PRP [39,40,42] and two studies with BM-MSCs [41,43] or BM-MNCs [41] were included. All included studies [39–43] ruled out patients with any type of uncontrolled active infection in the ulcer bed and patients with hepatic [39–41] or renal [41] insufficiency.

Table 3: Characteristics of the studies included in the systematic review of the effect of cell therapy on skin markers, healing time and adverse effects in adult patients with diabetic foot.

First author, year of publication and country	Participants (initial sample size and characteristics, dropouts, and final sample size)	Study design	Intervention	Results Cellular Therapy Group *Vs.* Control Group	Conclusions
Askø Andersen et al., [43], 2022, Denmark	n = 2 (2 ♂) Age (range): 68-70 years. DM I / II HbA1c < 97 mmol/mol, peripheral neuropathy, and presence of a DFU below the ankle measuring 0.25 cm ^{2} to 7.5 cm ^{2} BM-MSCs CD362 group n = 2 DFU Media in delayed healing of 4-52 weeks with conventional care Full supervision Study withdrawals: 0	Open-label, prospective, non-randomized 1:1 proof-of-concept study EudraCT number 2015-005580-16.	20-week follow-up 1 time 10.6 * 10 ^{6} autologous BM-MSCs (CD362) / 3 cm ^{2} Topical application	↓ Area ↑ Epithelializatio n ↑ Healing 2 AE (exudate)	Despite the common AEs found, the new topical BM-MSCs formulation is a safe and effective treatment option for DFUs.
De la Torre et al., [42] 2020, Spain	n = 4 (4 ♂) Age (range): 56-71 years DM I / II PRP Group n = 4 DFU Median healing delay of 17 months + 6 months with conventional care Full supervision Study withdrawals: 1	Prospective quasi-experimental study.	10-week follow-up 1 time/week 30 mL of blood. 1 centrifugation. 7–8 mL of autologous PRP. Gel: Autologous PRP + calcium chloride at 38 °C Topical application	↓ Area ↑ Epithelializatio n ↓ Average healing time. 1 AE (maceration)	PRP regenerates tissue and reduces the time to complete epithelializatio n and closure of DFUs refractory to conventional treatment.
Lu et al., [41], 2019, China	n = 41 (♂ ♀) Age (range) = 40-70 years DM II BM-MSCs n=20 limbs BM-MNCs n=21 limbs GC n= 41 limbs DFU Grade IV according to Fontaine classification, bilateral limb ischemia (ankle-brachial index = 0.30-0.60), necrosis unresponsive to conventional treatment Full supervision Withdrawals from the study: 12	Single-center, double-blind, randomized 1:1:1, placebo-controlled trial NCT00955669 clinicaltrials.gov	3 years of follow-up. 1 time. BM-MSCs 9.3 ± 1.1 * 108 / 20 mL Autologous CMN-MO 9.6 ± 1.1 * 108 / 20 mL Autologous GC: saline solution 20 mL VI 0.5 to 1 ml of CMBM-MSCs BM-MNCs or saline Intralesional application	↑* Healing rate ↔ Epithelializatio n ↓ Amputation rate 3 AE (edema)	Compared with conventional therapy, therapy with BM-MSCs and BM-MNCs promotes blood flow, ulcer healing, and reduces ulcer recurrence and amputation within 9 months.

First author, year of publication and country	Participants (initial sample size and characteristics, dropouts, and final sample size)	Study design	Intervention	Results Cellular Therapy Group *Vs.* Control Group	Conclusions
Orellano et al. [40], 2021, Uruguay	n = 6 (4 ♂ and 2 ♀) Age (range): 42-63 years DM I / II PRP-PG n = 3 PRP-G n = 3 DFU ≥ 2 cm ^{2}. Wagner II-III, mean healing delay 94 weeks, No closure after 12 weeks of treatment with conventional care Full supervision Study withdrawals: 0	Open, prospective, non-randomized observational study.	12-week follow-up 1 time/week. 48 applications in 6 patients 15-50 mL of blood. 2 centrifugations. Autologous PRP 1:3 Total blood volume Gel: PRP + 10% calcium gluconate at 37 °C. Intralesional or topical application in gel	↓* Area ↑ Epithelialization ↑ Healing No serious adverse effects were recorded.	DFUs resistant to standard treatment improved their epithelialization after the application of autologous PRP without adverse effects.
Smith et al. [25], 2020, UK	n = 12 (83% ♂ and 17% ♀) Age (range): 35-78 years DM I / II PRP-PG n=6 (83.33% ♂ and 16.67% ♀) GC n=6 (66.67% ♂ and 33.34% ♀) DFU > 25 mm ^{2} - < 10000 mm ^{2}, mean wound healing delay of 49 weeks with conventional care treatment Full supervision Study withdrawals: 0	1:1:1 randomized controlled trial NCT03085550 clinicaltrials.gov	12-week follow-up 1 time/week 52 mL whole blood + 8 mL of adenosine citrate dextrose acid. Hematocrit 8%. Autologous PRP gel CG: Standard podiatric wound care weekly Topical gel application	↓ Area ↑ Epithelialization ↑ Healing ↔ Healing time 3 AE (infection)	There were no differences between any of the groups in terms of clinical outcomes. This trial does not allow for recommendations on the clinical effectiveness of these treatments, and a larger RCT is needed to evaluate their efficacy.

Abbreviations: CG: control group; PRP: platelet-rich plasma; PRP-PG: puncture and platelet-rich plasma gel group; PRP-G: platelet-rich plasma gel group; BM-MSCs: bone marrow-derived mesenchymal stem cells; BM-MNCs: bone marrow-derived mononuclear cells; DM: diabetes mellitus; AE: adverse effect; HbA1c: glycated hemoglobin; DFU: diabetic foot ulcer; IV: intramuscular route; ↑: increase; ↓: decrease; ↑*: statistically significant increase; ↓*: statistically significant decrease; ↔: no significant difference; #: improvement; #*: statistically significant improvement.

Effect of cell therapy on cutaneous biomarkers in patients with diabetic foot ulcers

Four studies [39,40,42,43] evaluated the efficacy of regenerative therapy in reducing the area of chronic wounds resulting from DFU. Ulcers treated with PRP [40] administered topically by gel or gel plus intralesional injection achieved a significant ($p < 0.05$)

reduction in DFU area, with failure of standard therapy. Three studies [39,42,43] reported substantial but non-significant ($p > 0.05$) reductions in DFU area and volume [39]. Epithelialization [39,40,42,43], wound healing [39,40,43], and healing time [42] were non-significantly increased ($p > 0.05$) after the use of PRP [39,40,42] or BM-MSCS [43] cellular therapy. The overall healing rate was significantly improved ($p < 0.05$) compared to the control group (CG) after application of BM-MSCs or BM-MNCs [41]. Treatment with MSC-BM or CMN-BM was able to non-significantly reduce the amputation rate [41] compared to the CG (Table 3).

Adverse effects resulting from the use of cell therapy in patients with diabetic foot ulcers

A total of nine adverse effects (AEs) have been described in association with cell therapy, 5 in studies using CM [41,43] and 4 in studies using PRP [39,42]. However, none were classified as serious AEs and they disappeared after the first intervention [39,41–43]. The AEs were edema [41], infection [39] in the ulcer area (which resolved after the application of antibiotics), exudate [43] that resolved with a dressing change, and maceration in the perilesional area [42] of the wound. The study conducted by Orellano et al. [40] did not report any AEs (Table 3).

DISCUSSION

The purpose of this systematic review was to evaluate the potential of therapies including BM-MSCs, BM-MNCs, and PRP in diabetic patients suffering from DFUs with complex care requirements unresponsive to conventional treatment. Five studies [39–43] met the inclusion/exclusion criteria. Overall, the results showed a significant reduction in size [40] and a significant improvement in the healing rate [41] of DFUs. In addition, notable improvements in DFU epithelialization [39,40,42,43] and healing [39,40,43] have been reported, although clear evidence of a decrease in healing time has not been demonstrated [39,42]. No serious AEs were reported, only some mild ones [39,41–43].

DFUs are the result of an imbalance in metalloproteinases (MMPs) and MMP inhibitors, exacerbated by deprivation of oxygen and essential nutrients to the injured tissue due to diabetic neuropathy and vasculopathy [5]. This situation disables epithelial cells to produce healing agents such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), hindering normal wound healing [44,45]. Overall, healing is altered, presenting a prolonged inflammatory phase, defects in the remodeling of the extracellular matrix, formation of free radicals, inhibition of the synthesis of cell growth factors and the release of factors that favor the migration of cells of the immune system [40]. To combat these disorders in DFU healing, PRP, with a platelet concentration higher than the basal level, stimulates natural healing responses mediated by the release of growth factors such as PDGF, VEGF, platelet factor 4 (PF4), interleukin 1 (IL-1), platelet-derived angiogenic factor (PDAF), epidermal growth factor (EGF), platelet-derived endothelial growth factor (PDEGF), epithelial cell growth factor (ECGF), insulin-like growth factor (IGF), osteocalcin, osteonectin , fibrinogen, fibronectin and thrombospondin (TSP) or transforming growth factor beta 3 (TGF-ß3), thus promoting cell differentiation and proliferation, consequently facilitating the formation of new cells (46) . These growth factors promote angiogenesis and nutrition of cells in ischemic tissues [45,47]. Furthermore, PRP serves as a defense mechanism at the ulcer site through two pathways: on the one hand, it provides leukocytes present in the PRP

itself and on the other hand, it collaborates in opsonization by attracting macrophages [44].

BM-MSCs or BM-MNCs offer a versatile approach due to their ability to differentiate into a variety of cell types such as osteoblasts, chondroblasts and nerve cells, making them ideal for the repair and regeneration of damaged tissue. [48] . The therapeutic potential of BM-MSCs or BM-MNCs in the treatment of DFU ischemia is through the secretion of VEGF, fibroblast growth factor 2, angiopoietin-1 and the ability to differentiate endothelial cells, vascular cells and smooth muscle cells into angioblasts [49]. Iwase et al. have described that BM-MSCs AND BM-MNCs promote a remarkable angiogenesis and a substantial increase in blood flow to ischemic lower limbs [50].

On the other hand, the activation and migration of keratinocytes would be involved in the epithelialization process of UPD [11]. Stem cells could increase the expression of early keratinocyte activation markers, such as keratins 6, 16 and 17 [51]. In addition, stem cell-based therapy could stimulate cell proliferation by inducing an imbalance in genes related to the cell cycle with a decrease in the expression of the retinoblastoma protein family (Rb, p107 and p130) and increase the expression of CDC2, cyclin B1, cyclin D2, cyclin A2, cyclin F and cyclin M4, promoting the increase of CDC2/cyclin B1 and CDC2/cyclin A2 complexes that promote G1/S and G2/M transitions in the cell cycle, in addition to the decrease in the expression of CHES1 and WEE1 [52]. These processes could provide a better structural matrix of the connective tissue to increase cell adhesion and proliferation, thus enhancing the results of the healing process of DFUs.

However, cell-based regenerative therapies are not exempt from producing AEs [53]. In four [39,41–43] of the studies included in the present systematic review, mild and rapid-onset AEs were found, causing a non-significant worsening of the initial ulcer, 5 AEs in studies with stem cells [41,43] and 4 AEs in studies using PRP [39,42]. These AEs are like those that appeared after the infusion of BM-MSCs for the treatment of Dystrophic Epidermolysis Bullosa and disappeared after 24 hours [54]. The use of BM-MSCs or BM-MNCs in cell therapy may increase susceptibility to infections, given their immunosuppressive effects, cell embolism by secretion of tissue factors and other coagulation activation proteins, acute or chronic immunogenicity of the cells themselves and neoplastic potential due to their proliferative capacity [48].

Limitations and strengths

The authors acknowledge some limitations. First, a limited number of manuscripts met the inclusion criteria. Second, the high heterogeneity of the results due to the diversity of ulcer characteristics and their pathophysiology (PAD, neuropathy, and infection) prevents a meta-analysis and requires caution regarding the results presented in this review. However, the systematic approach followed the PRISMA method [34], the search was performed using four databases relevant to the study topic: CUIDEN, WOS, Medline (PubMed), and Scopus, and DeCS search terms were used. [35] and MesH [36] . In addition, the McMaster methodological quality assessment tool was used [38] to ensure that all selected records met minimum quality criteria and the systematic review was registered in PROSPERO (#CRD 42024504290).

Practical implications

Non-healing DFUs typically lack any effective treatment; however, a novel regenerative medicine therapy with SC or PRP could help with non-healing DFUs, according to the results of our review. This study demonstrates that SC or PRP therapy, as an add-on therapy for DFUs, can provide significant clinical benefits, particularly in wound repair, epithelialization, and healing. We have described the safety and efficacy of SC or PRP as a novel approach to DFU treatment compared with standard treatment. While further research is required, preliminary results are encouraging and suggest that this therapy may significantly improve wound healing and quality of life in patients with diabetes. The findings of this study not only have significant implications for practice in the multidisciplinary management of DFUs but also carry important considerations for policy and clinical decision-making. Nursing staff and other healthcare professionals are crucial for the effective treatment and management of DFUs, providing direct patient care, administering SC or PRP treatments, and monitoring wound progression. Their role in patient education on wound care, glycemic control, and lifestyle modifications is vital to prevent complications and promote healing. From a policy perspective, it is essential that health systems prioritize comprehensive strategies for DFU management. This includes funding and supporting ongoing training for healthcare professionals in the latest treatment modalities for DFUs, as well as patient education programs.

Recommendations

The general recommendation process for cellular therapy for DFUs could be established as i) Collection and preparation of SC or PRP: These cells can be obtained from different sources, such as bone marrow, fat, or umbilical cord. They are then prepared in a laboratory, where they are expanded and selected for use in the therapy; ii) Administration of SC or PRP is directly into the ulcer area, either by injection, topical application, or using a vehicle such as a biomaterial; iii) Stimulation of healing: Once at the wound site, SC or PRP release growth factors that promote angiogenesis, endothelial cell proliferation, and repair of damaged tissue; iv) Monitoring and evaluation: The patient is regularly monitored to assess the response to treatment and possible side effects.

Furthermore, there are advantages derived from the application of cell therapy in DFUs, such as a higher healing rate because cell therapy can accelerate the healing process and increase the chances of the ulcer healing completely, a reduction in the need for amputations in patients with DFUs, and a significant improvement in the quality of life of patients with diabetes, as it allows them to walk and perform daily activities without pain. However, regenerative medicine through SC or PRP must overcome some challenges and limitations. In this sense, the cost of cell therapy may limit its access for some patients. Further research is needed with studies to determine the long-term efficacy and safety of cell therapy for DFUs. In addition, potential side effects such as inflammatory or infectious reactions at the administration site must be considered.

CONCLUSION

This review provides compelling evidence that regenerative medicine based on BM-MSCs, BM-MNCs, and PRP in diabetic patients suffering from DFUs with complex care requirements unresponsive to conventional treatment is effective, safe, and multi-benefit

treatment. Cell therapy significantly reduces DFU size and shows a significant improvement in DFU healing rates, with substantial benefits for epithelialization and wound healing. Importantly, its use is safe and shows no serious adverse effects.

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Conflict of interest

The authors declare no conflict of interest.

Authors' Contributions

DFL: (Corresponding author) conceived and designed the study, analyzed and interpreted the data, wrote the paper, wrote the original draft, prepared figures and/or tables, and approved the final draft submitted for publication; CJF: wrote the paper, analyzed and interpreted the data, and critically revised the article; MCSM, SRG, and ABDP: analyzed and interpreted the data and critically revised the article.

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