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Scoping Review of Hydrogel Therapies in the Treatment of Diabetic Chronic Wounds

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Background: Chronic diabetic wounds are a significant issue that can be treated with topical hydrogel therapies. The aim of this study was to review the different compositions of hydrogel that have been developed and analyze their clinical relevance in the treatment of chronic diabetic wounds.
Methods: We conducted a scoping review in which twelve articles were selected for review after applying relevant inclusion and exclusion criteria using a two-reviewer strategy. Data extracted from these studies was used to answer the following research question: What is the composition of hydrogels used to treat chronic diabetic wounds and how effective are they?
Results: We analyzed five randomized controlled trials, two retrospective studies, three reviews, and two case reports. Hydrogel compositions discussed included mesenchymal stem cell sheets, carbomer, collagen, and alginate hydrogels, as well as hydrogels embedded with platelet-derived growth factor. Synthetic hydrogels, largely composed of carbomers, were found to have high levels of evidence supporting their wound healing properties, though few articles described their routine use in a clinical setting. Collagen hydrogels dominate the present-day hydrogel market in the clinical treatment of chronic diabetic wounds. The augmentation of hydrogels with therapeutic biomaterials is a new field of hydrogel research, with studies demonstrating promising early in vitro and in vivo animal studies demonstrating promising early results for in vitro and in vivo animal investigations.
Conclusions: Current research supports hydrogels as a promising topical therapy in the treatment of chronic diabetic wounds. Augmenting Food & Drug Administration-approved hydrogels with therapeutic substances remains an interesting early area of investigation. *(Plast Reconstr Surg Glob Open 2023; 11:e4984; doi: 10.1097/GOX.0000000000004984; Published online 26 May 2023.)*

INTRODUCTION

Chronic, nonhealing wounds place a significant burden on modern-day healthcare systems, with estimated annual costs between $28.1 and $96.8 billion dollars in developed nations.[1] Chronic wounds are often related to comorbid conditions, such as diabetes mellitus, vascular disease, and kidney disease. They may also arise secondary to trauma or limited mobility leading to pressure sores. Diabetes mellitus, specifically, is a leading cause of nonhealing wounds in the United States, with diabetic patients having an estimated 15%–25% lifetime risk of developing a chronic wound.[2]

Wound care for these chronic nonhealing wounds is complex. It usually involves both debridement, which can be autolytic/enzymatic or surgical/mechanical, and the application of a variety of dressings. Initially, dry dressings and gauze were used to simply to cover the wound, but the lack of moisture often prevented wound healing. Additionally, dry dressings adhere to a wound, making dressing changes painful. More recently moist, occlusive dressings have been used prevent microbial invasion and retain moisture. These dressings, however, do not target other causes of delayed wound healing, such increased inflammation or cellular dysfunction.[3]

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A more advanced option for wound care is hydrogels, which can act as a vehicle for drug delivery that can target components of the wound healing and inflammatory cascades. Hydrogels have a three-dimensional structure that can hold fluids while maintaining integrity making them ideal drug carriers. Hydrogels can also retain a moist environment while absorbing exudate that the chronic wound may release, thus having the advantage of being only partially occlusive. Hydrogel therapy has become of significant interest for wound healing, with the first clinical trials of hydrogel therapy starting in the late 1990s.[4,5] Hydrogels are broadly divided into two groups: synthetic polymers and natural/biologic polymers.

Synthetic hydrogels can be composed of polymers such as acrylate, polyethylene oxide (PEO), polyvinyl alcohol (PVA), polyacrylic acid (PAA), and polypropylene fumarate-co-ethylene glycol (P (PF-coEG).[6] Synthetic polymers are widely and cheaply available, making them an economic choice for wound care in patients. However, synthetic materials lack natural cell adhesion sites and chemoattractants. These synthetic hydrogels require chemical modification to promote cell adhesion.[7,8] Platelet-derived growth factor (PDGF) or stem cells can be included to form hydrogels that promote wound healing and accelerate cell proliferation.[9,10]

Biologic hydrogels are composed of proteins and polysaccharides such as collagen, gelatins, cellulose, fibrin, alginate, and agarose. Inherent bioactivity and biocompatibility make these an ideal choice for topical wound healing. Collagen, a structural element of the extracellular matrix, has inherent properties that promote cell proliferation, differentiation, and repair. While collagen promotes tissue healing and regeneration, it can also be used in the delivery of drugs to a specific site. Fibrin hydrogels take advantage of the clotting properties of fibrin, forming a natural, protein-based polymer.[11] Compared with synthetic hydrogels, biologic hydrogels have limited tunability and increased risk of an immunogenic reaction.[12]

Hydrogel therapy for wound management has been well-established, and there are currently several forms of hydrogels available. The efficacy of different compositions has yet to be established and compared, making it difficult to determine which hydrogel therapies are most beneficial in the setting of chronic diabetic wounds. Additionally, hydrogels hold promise in the delivery of pharmaceuticals and optimizing wound healing. We performed a scoping review investigating the use of hydrogels for diabetic wound healing to define their current use and identify data supporting their efficacy and safety.

Takeaways

Question: What is the composition of hydrogels used to treat chronic diabetic wounds and how effective are they?

Findings: Current research supports hydrogels as a promising topical therapy in the treatment of chronic diabetic wounds. The augmentation of hydrogels with therapeutic biomaterials is a new field of hydrogel research, with studies demonstrating promising early results for in vitro and in vivo animal investigations.

Meaning: Augmenting Food & Drug Administration-approved hydrogels with therapeutic substances remains an interesting early area of investigation, and a promising potential therapy in the treatment of chronic diabetic wounds.

METHODOLOGY

Following the scoping review technique described by Arksey and O'Malley,[13] we developed the following research question: how often are hydrogels used to treat chronic wounds in the clinical setting and how effective are they? We then identified the relevant studies using inclusion (topical hydrogel therapy and diabetic patients) and exclusion (animal studies, in vitro studies, and studies not written in English) criteria (Fig. 1). A total of 284 unique articles were extracted from two databases, PubMed and Web of Science, published between 1990 and 2022. Candidate articles were extracted and verified by two independent reviewers, and disagreements were ameliorated through consensus. The following search criteria were used to identify relevant articles: ((((diabetes mellitus) OR (diabetes)) OR (diabetic)) AND (hydrogel)) AND (topical) OR ((hydrogels[Title]) OR (hydrogel[Title])) AND ((diabetes[Title]) OR (diabetic[Title])). A comprehensive search strategy is listed in Supplement Digital Content 1. (**See Supplemental Digital Content 1,** which shows the comprehensive search strategy. **http://links.lww.com/PRSGO/C600**.) Studies were analyzed using Covidence, where two reviewers independently screened, filtered, and categorized each article retrieved (Fig. 2). Outcomes measures included participant volume, wound closure rates, time to wound closure, and adverse events, if any. Levels of evidence and the presence of study bias were also ascertained.

RESULTS

We analyzed five randomized controlled trials, two retrospective studies, three reviews, and two case reports.

Stem Cell Sheet Hydrogels

Mesenchymal stem cells (MSCs) are naturally found in the skin and aid in wound repair, making them a favorable vehicle for wound healing, as demonstrated by Zeng et al in a case study that successfully treated a diabetic patient's plantar ulcer over a period of 3 weeks.[14] In a similar vein, allogeneic adipose-derived stem cells (ASCs) are commercially available in the form of a dermal substitute. ASCs are derivatives of MSCs and have similar properties with the potential to accelerate wound healing. When fashioned into allogeneic sheets, ASCs and MSCs can secrete their own extracellular matrix (ECM) that is of diverse composition not found in other biological hydrogels. A randomized controlled trial (RCT) conducted by Moon et al compared MSC hydrogel to polyurethane film (control) and found that

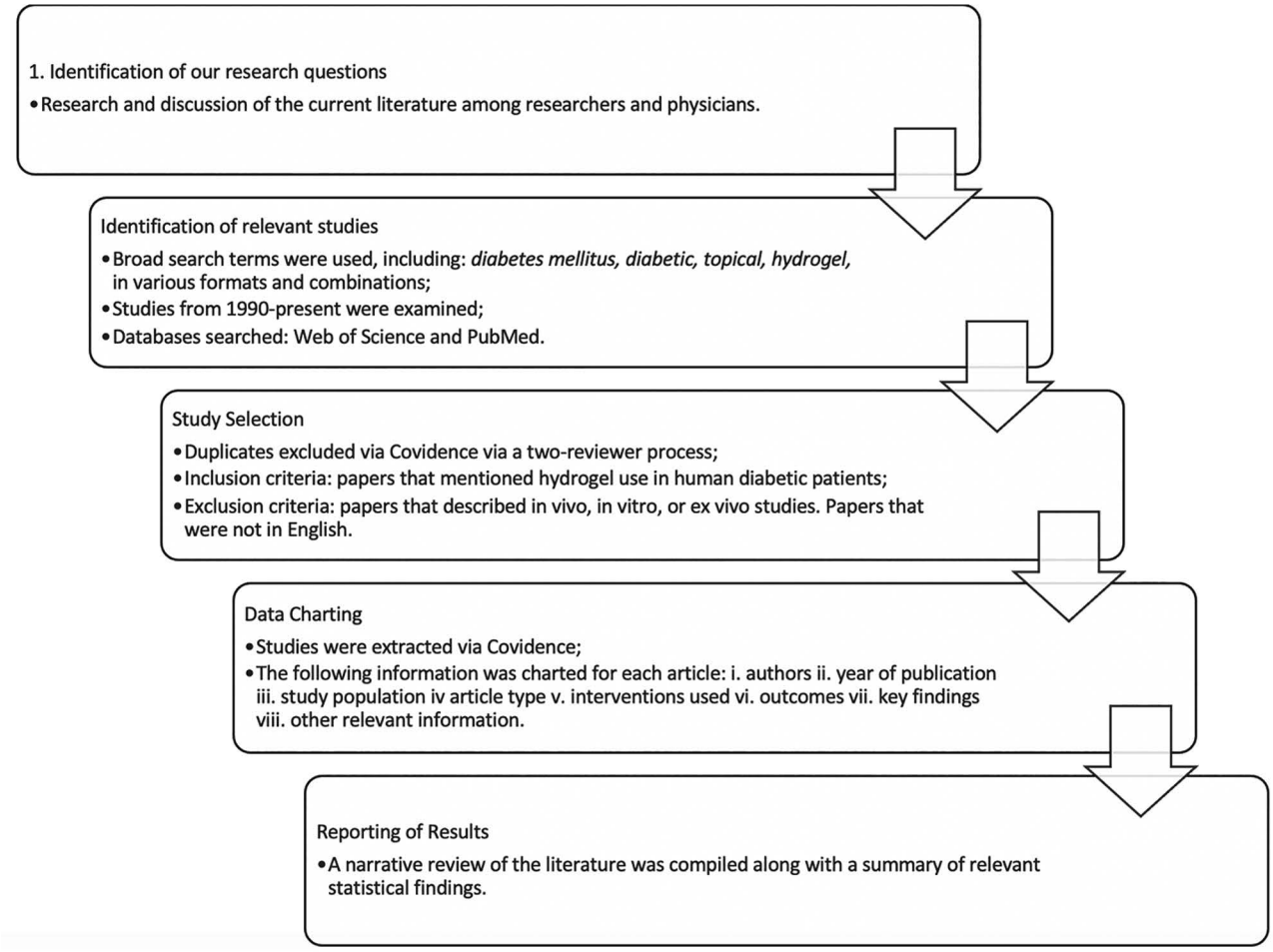

Fig. 1. A five-step approach to the scoping review.

complete wound closure occurred in 73% of the treatment group and only 47% of the control group at week 8, and 82% and 53% at week 12, respectively. The median time to closure was 28.5 days and 63 days for treatment and control groups, respectively. No adverse events were reported in either group.[15]

Carbomer Hydrogels

Carbomers are a series of polymers derived from acrylic acid that are commercially used as thickeners in topical agents and can be used to create hydrogels that are acceptable carriers for the release of drugs. A retrospective study by Vaseenon et al examined 20 patients that received a combination of synthetic acrylate hydrogel, contact cast, and foam dressing for the management of plantar ulcers. The study found that 95.2% of the patients healed completely in a mean time of 30.1 days, and only one patient developed severe infection requiring amputation.[16]

Carbomer hydrogels can also be loaded with pharmaceuticals to deliver drugs in a controlled manner over time. Erythropoietin (EPO) is an angiogenic factor that upregulates the transforming growth factor-beta pathway. Hamed et al are conducting an ongoing RCT assessing the safety of RMD-G1, a topical carbomer-based hydrogel with a fibronectin matrix that secretes EPO as its active ingredient. Interim results of the trial published in 2019 show that the treatment group saw a statistically significant reduction in the wound areas compared with control, and RMD-G1 was a safe treatment when compared with standard of care.[17]

An RCT by Gallelli et al examined a nano-hydrogel, a more tightly cross-linked hydrogel, carbomer embedded with quercetin and oleic acid as a novel treatment for diabetic foot ulcers. Quercetin and oleic acid are flavonoids that accelerate the acute phase of wound healing and modulate the immune response. The treatment group that received a flavonoid-embedded hydrogel treatment had a statistically significant reduction in wound healing time when compared with the control group, who only received hyaluronic acid treatment. No adverse reactions were reported.[18]

Phenytoin (PHT), while traditionally used as an anti-seizure medication, has wound healing properties when applied topically and released slowly.[19] An RCT by Motawea et al analyzed the effects of nano-hydrogel lipid carbomer carriers (NLC) embedded with PHT in diabetic foot ulcers. Wounds treated with the PHT-NLC hydrogel demonstrated a smaller wound area when compared with

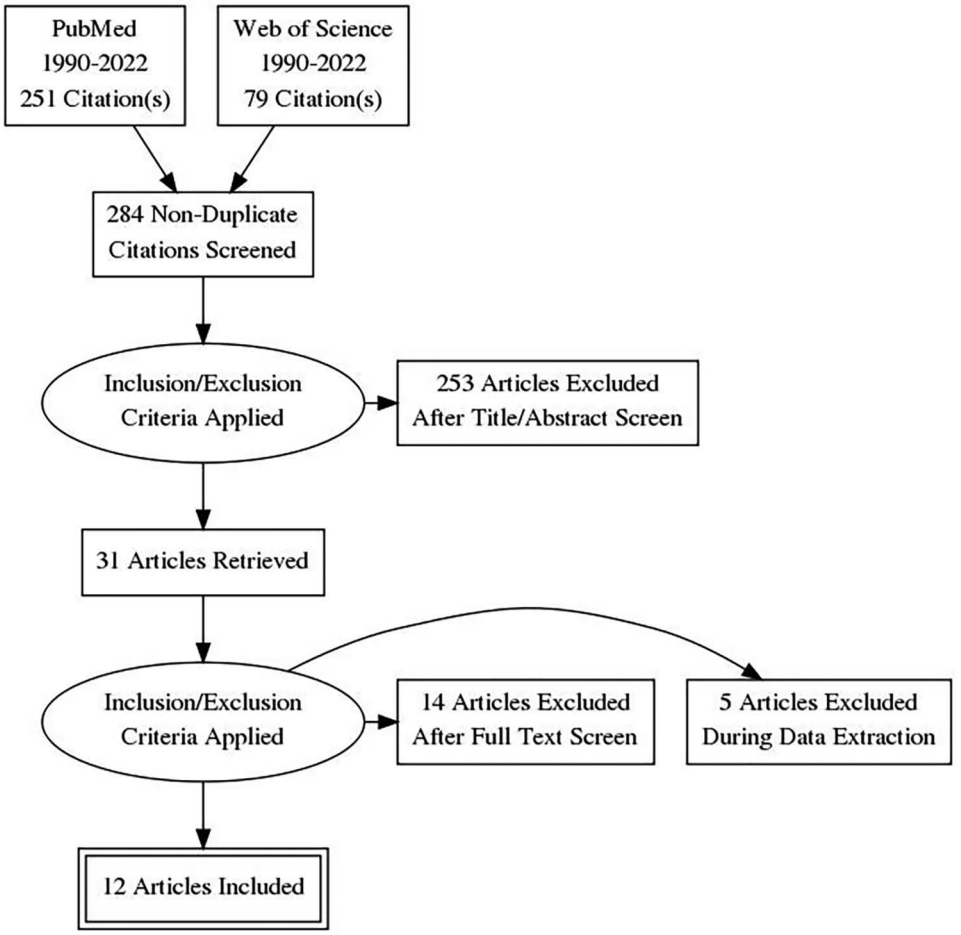

Fig. 2. PRISMA schematic of scoping review article extraction strategy.

control groups, which were blank hydrogel or topical PHT spray. There was also an overall reduction in the size of the ulcer overtime in the treatment group when compared with both control groups.[20]

Collagen Hydrogels

Collagen is a widely utilized substrate of hydrogels. A review by Reyes-Martinez et al found that while Apligraf and Dermigraft are the only two Food & Drug Administration (FDA)-approved collagen-based hydrogels, there are many other types of hydrogels in their nascent stages of testing.[21] An RCT by Nilforoushzadeh et al studied a skin graft with stromal vascular fraction cells encapsulated in fibrin-collagen hydrogel. They found a statistically significant increase in the skin thickness and vascular density in the stromal vascular fraction group versus control.[22]

Alginate Hydrogels

Gustinelli et al conducted a retrospective study in which seven patients were treated with alginate hydrogel enriched with fatty acids and vitamins A and E. Two patients had complete wound healing, and all patients had a reduction in the size of the lesion. Additionally, using the Pressure Ulcer Scale for Healing score to assess improvement, the authors noted the mean Pressure Ulcer Scale for Healing scores decreased from 9.8 to 6.6 during the study.[23]

Platelet-derived Growth Factors

A meta-analysis conducted by Dumville et al studied the statistical significance of multiple studies that looked at hydrogels alone, as well as hydrogels that incorporated PDGFs embedded into a synthetic hydrogel. The authors found there was a moderate level of evidence supporting the use of hydrogels over basic wound dressings.[21] Low levels of evidence were found supporting the use of hydrogels over topical PDGF therapy. Reyes-Martinez et al reviewed the FDA-approved options for PDGF hydrogels, and found that Leucopatch (now known as 3C Patch) (Reapplix ApS, Birkerød, Denmark) and Regranex (Smith & Nephew, Watford, Hertforshire, United Kingdom) are two FDA-approved and commercially used topical wound therapy treatments approved for use in diabetic ulcers.[24] Leucopatch has been studied with a multicenter clinical study examining outcomes in patients that demonstrates accelerated wound healing when compared with standard of care. There are concerns regarding the availability of this treatment, as it requires a specialized centrifuge and skilled healthcare workers for onsite administration.[25]

Table 1. Randomized Controlled Trials

Study	Author	Year	Participants	Intervention	Outcomes
Potential of allogeneic adipose-derived stem cell-hydrogel complex for treating diabetic foot ulcers	Moon et al[15]	2019	39 participants Control group (polyurethane film) = 22 Treatment group (MSC hydrogel) = 17	MSCs–hydrogel complex	Complete wound closure in 73% of the treatment group and 47% of the control group at 8 wk. Complete wound closure was achieved in 82% of the treatment group and 53% of the control group at 12 wk. Median time to closure was 28.5 and 63.0 d for the treatment group and the control group, respectively. No adverse events were reported in either group related to wound care treatment
Interim results of the remede d'or study: a multicenter, single-blind, randomized, controlled trial to assess the safety and efficacy of an innovative topical formulation of erythropoietin for treating diabetic foot ulcers.	Hamed et al[19]	2019	10 participants Control group (standard of care) = 5 Treatment group (EPO hydrogel) = 5	RMD-G1, a topical carbopol-based hydrogel with a fibronectin matrix whose active ingredient is erythropoietin (EPO)	Interim results reveal that those diabetic foot ulcers that were treated with RMD-G1 responded positively: there was a significant reduction in the wound areas ($P < 0.01$)
Nano-hydrogel embedded with quercetin and oleic acid as a new formulation in the treatment of diabetic foot ulcer: A pilot study.	Gallelli et al[18]	2020	56 participants Control group (0.2% hyaluronic acid) = 28 Treatment group (Nano-hydrogel) = 28	Nano-hydrogel embedded with quercetin and oleic acid	The treatment group had a significant reduction healing time compared with control ($P < 0.01$). No adverse reactions were noted
Engineered skin graft with stromal vascular fraction cells encapsulated in fibrin-collagen hydrogel: A clinical study for diabetic wound healing.	Nilforoushzadeh et al[22]	2020	10 participants Control group (non-vascularized skin grafts) = 5 Treatment group (Collagen hydrogel) = 5	Stromal vascular fraction cells encapsulated in fibrin-collagen hydrogel	There was a significant ($P \leq 0.05$) increase in skin thickness and density in the vascular beds of the hypodermis measured with skin scanner compared with control
The impact of topical phenytoin-loaded nanostructured lipid carriers in diabetic foot ulceration.	Motawea et al[20]	2019	27 participants Negative control group (blank hydrogel) Positive control group (topical PHT) Treatment group (PHT-NLC hydrogel)	Patients either received topical phenytoin (PHT), phenytoin imbedded in a nanoparticle lipid carrier (PHT-NLC) hydrogel, or a blank hydrogel	Wounds treated with PHT-NLC hydrogel showed smaller wound area compared with control ($P < 0.05$). The overall reduction in ulcer size were 95.82 ± 2.22% for PHT-NLC-hydrogel in comparison with 47.10 ± 4.23% and 34.91 ± 28.33% for PHT and blank hydrogel ($P < 0.001$), respectively

Clinical studies demonstrated statistically significant accelerated wound healing for experimental groups treated with Regranex in NaCMC hydrogel.[26] In 2018, however, Smith & Nephew conducted a pharmacologic safety study that found an increased rate of malignancy in patients treated with three or more tubes of Regranex. This was later disproved by multiple safety studies controlling for confounding factors.[27] (Tables 1–4).

DISCUSSION

After reviewing randomized controlled trials, retrospective studies, reviews, and case studies over the past 30 years, it remains clear that research into hydrogels for diabetic wound healing is in its nascent stage. We found high levels of evidence that chronic diabetic foot wounds treated with blank synthetic and biologic hydrogels have increased wound closure rates and shorter healing times; however, the evidence for hydrogels as a scaffold to deliver other bioactive ingredients remains less clear.[15,16,18,21,22] Nonetheless, there are several promising hydrogels in development.

Currently, collagen-rich hydrogels dominate the healthcare market. Collagen is a structural element of the extracellular matrix and has inherent properties that promote cell proliferation, differentiation, and repair. The most well-studied collagen-rich hydrogels have been developed into commercial products, such as Apligraf (Organogenesis, Canton, Mass.) and Dermagraft (Smith & Nephew, Watford, Hertforshire, UK).[21]

Carbomer-based hydrogels are also widely studied, though randomized controlled trials are relatively recent and their introduction into clinical practice is limited. Acrylate hydrogels alone, carbomer-based hydrogels without embedded pharmacotherapies, promote cell regeneration while simultaneously allowing for autolytic debridement.[28] A study by Matzen et al in 1999 compared Coloplast hydrogel (Owens & Minor, Richmond, Va.), a synthetic carbomer hydrogel, to standard of care and found that complete healing occurred at a statistically

Table 2. Retrospective Studies

Study Title	Authors	Year	No. Patients	Study Design	Intervention	Outcome
Off-loading total contact cast in combination with hydrogel and foam dressing for management of diabetic plantar ulcer of the foot.	Vaseenon et al[16]	2014	20 patients (21 ulcers)	Retrospective study with prospective data collection between September 2010 and August 2012	Contact cast plus hydrogel and foam dressings	Twenty (95.2%) healed completely in a mean of 30.1 d (14–70 d). One patient who had an unhealed ulcer developed a severe infection 2 mo after treatment, requiring below the knee amputation. There were three cases of recurrence of the ulcers after casting
Effects of hydrogel with enriched sodium alginate in wounds of diabetic patients.	Gustinelli Barbosa et al[23]	2018	7 patients	Retrospective study of patients supervised from April to July 2017 via clinical history, photographic record, planimetry, and classification of the wound severity by the Pressure Ulcer Scale for Healing (PUSH) system	Hydrogel with sodium alginate enriched with fatty acids and vitamins A and E	Two patients had complete wound healing, but all presented a reduction of the lesion area of approximately 22.2% and PUSH score of 9.8–6.6

Table 3. Reviews

Study	Authors	Year	Intervention/Participants	Study Design	Outcomes
Hydrogel dressings for healing diabetic foot ulcers.	Dumville et al[21]	2013	Basic wound dressing versus hydrogel: 198 patients (three studies) Larval therapy versus hydrogel: 140 patients (1 study) Platelet-derived growth factors versus hydrogel: 104 patients (1 study)	Systematic Review comparing hydrogel dressings to other topical dressings in the treatment of diabetic foot ulcers	Moderate level of evidence supporting the use of hydrogels over basic wound dressings. Low levels of evidence supporting the use of hydrogels over topical platelet-derived growth factor therapy and larval dressings. Little to no evidence in the comparison of intrasite hydrogels and Purilon hydrogels
Advanced hydrogels for treatment of diabetes.	Reyes-Martínez et al[24]	2019	Hydrogels	A review on hydrogels used for diabetes, including laboratory success and commercial products approved by the FDA	Apligraf, Leucopatch, and Regranex are currently the only three FDA-approved hydrogels used for diabetic wound care as of the date of publication.
Functional hydrogels for diabetic wound management.	Gao et al[29]	2021	Hydrogels	Review of the properties of hydrogels, including bactericidal and wound healing promotive effects	A successful all-in-one wound treatment hydrogel that combats biofilms and minimizes the effects of diabetes has not yet been developed. Certain single-function hydrogel dressings, such as antifouling, antibacterial, and pro-healing can target specific issues. Successful application of the hydrogels to clinical treatment of diabetic ulcers remains challenging with only a few clinical trials in their early stages

Table 4. Case Studies

Study Title	Authors	Year	No. Patients	Case	Intervention	Finding
A diabetic foot ulcer treated with hydrogel and hyperbaric oxygen therapy: a case study.	Aguiar et al[30]	2017	1	Presence of a bullous wound on the left great toe that led to an amputation of the first and second left toes	After completing the normal treatment and the removal of a bacterial infection in the lesion, the patient underwent a treatment that was based on an alginate hydrogel (0.9% saline solution) and hyperbaric oxygen therapy	After 60 sessions of the therapy, almost complete closure of the wound was observed
Three-week topical treatment with placenta-derived mesenchymal stem cells hydrogel in a patient with diabetic foot ulcer: a case report.	Zeng et al[14]	2017	1	A wound bed located over the dorsalis pedis of the right foot	Placenta-derived mesenchymal stem cell-hydrogel dressing changed everyday for 3 wk	The patient's foot ulcer was almost healed, and foot function in walking was well preserved. No complications were observed. No recurrence occurred in the subsequent 6 mo.

higher rate using Coloplast. They found a lower ulcer volume and less need for repeat debridement overall.[31] Despite this success, today Coloplast independently markets the FDA-approved Woun'Dres Carbomer-Collagen Hydrogel (Coloplast, Humlebæk, Denmark), which is not the same hydrogel used in the original RCT. Instead, their new collagen and carbomer biologic hydrogel highlights the trend that is seen in hydrogel research shifting toward the use of biologic compounds, such as collagen, over synthetics. The shift to biologics is due to the advantages of biocompatibility and inherent bioactivity that have the potential to accelerate wound healing.

However, the major advantage of synthetic composition of carbomer hydrogels is the ability to augment them with therapeutic biomaterials. When embedded with EPO, carbomer hydrogels possesses the ability to suppress inflammation and apoptosis while promoting epithelialization and collagen formation. In vitro and in vivo animal studies have shown that cellular exposure to EPO allows for enhanced differentiation of myofibroblasts and accelerated wound closure.[32] While the RCT by Hamed et al showed promising results in humans, it remains important to note that there are no FDA-approved, commercially marketed EPO-releasing topical agents or hydrogels.[17] PDGFs enmeshed in synthetic hydrogels, such as Leucopatch and Regranex, have strong evidence supporting their use in diabetic wounds, are FDA-approved, and are commercially available.[24] Nano-hydrogels are carbomer hydrogels that can be impregnated with flavonoids, as shown by Gallelli et al. This trial remains open, and more research is required before FDA approval.[18]

Topical PHT, another drug being investigated for hydrogel augmentation, is commercially available as a spray, which is shown to accelerate wound healing by promoting collagen deposition, nerve regeneration, and fibroblast proliferation while exhibiting anticollagenase and antibacterial activity.[19] Unfortunately, the spray has limitations due to the high concentrations of organic solvents that can cause skin irritation if applied directly to the skin.[33] Synthetic hydrogel as a vector for more controlled PHT delivery has had promising results in humans but is not FDA-approved.

The biology of stem cells makes them an appealing additive to hydrogels to improve wound healing. In vitro studies have shown that MSCs exhibit secretory activity and can actively inhibit proinflammatory cytokines such as TNF-alpha, interleukin (IL)-6, IL-8, IL-1, and intracellular adhesion molecule as well as promote the secretion of anti-inflammatory cytokine IL-10.[8–10] MSCs have been shown to promote high degrees of granulation tissue formation, epithelialization, and angiogenesis in vitro and in vivo animal studies, which are all markers of ideal wound healing.[34] Unfortunately, MSCs are not commercially available and are cost-prohibitive, making it difficult to treat patients with MSC-embedded hydrogel.

It is important to note that the drug-eluting hydrogels reviewed have a low level of evidence to support their use. There is currently no FDA-approved or commercially marked hydrogel that is impregnated with a pharmaceutical that is released overtime topically. There are several factors contributing to the relatively low levels of clinical evidence for these types of hydrogels despite a large amount of in vitro and in vivo work.[35] The kinetics of drug-eluting hydrogels are difficult to study and, given that the composition of hydrogels as well as the size and structure of drugs of interest can vary greatly, studying the wide variety of possibilities remains elusive. Additionally, the exact dosage of a drug that needs to be released over a given period has not yet been determined. Tailoring hydrogels to meet these complex needs is an area of ongoing research.[36]

The main limitation of this review is potential patient selection bias in the studies published. Additionally, heterogeneity in the outcome measures, adverse events, and complications reported make it difficult to compare studies directly. Few studies discussed adverse events, and these were limited to recurrence of ulcers and new site abrasions.[16] Reported complications were most frequently due to infections, which are a well-known complication of diabetic foot ulcers. Finally, chronic diabetic wounds can have devastating long-term consequences for patients and significantly impact our modern-day healthcare system. Biologic and synthetic hydrogels are widely used in clinical practice, but loading these hydrogels with biomaterials that accelerate healing is a promising area of research. Although there is in vitro and in vivo research demonstrating that hydrogel scaffolds impregnated with bioactive ingredients have wound healing properties and can potentially provide controlled release of pharmaceuticals, there is limited translation to clinical practice. Continued high-quality studies are needed to transition these hydrogel therapies for diabetic lower extremity wounds from bench to bedside.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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