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HYDROGEL-BASED WOUND DRESSING IN THE TREATMENT OF DIABETIC FOOT ULCERS: A NARRATIVE REVIEW.

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ABSTRACT

Background. Diabetic foot ulcers (DFUs) are a common and highly morbid consequence of long-standing and poorly managed diabetes. This case study aims to determine the effectiveness of HBWD in the treatment of diabetic foot ulcers (DFU) in diabetic patients.
Methods. The method in this case study is an evidence-based case report. The clinical question used: Are HBWD effective in the treatment of DFU, especially in limited-resource healthcare facilities? To answer this question, we searched the evidence from PubMed, Cochrane Database, Semantic Scholar, and Google Scholar with various keywords based on the clinical question. The studies were selected based on pre-determined inclusion and exclusion criteria and were critically appraised.
Results. Four randomized controlled trials (RCTs) that met the inclusion and exclusion criteria were found. There was no significant difference in the reduction of ulcer area (RUA) rate or complete wound closure (CWC) rate in all RCTs. When compared to the control or non-hydrogel group, three studies reported some favoring aspects in the HBWD group, such as fewer inflammatory signs and faster CWC meantime.
Conclusion*. HBWD is recommended in the treatment of DFU because they are widely available, cost-effective, and relatively easy to use.*

Keyword: *Hydrogel, Wound Dressing, Diabetic Foot Ulcer*

ABSTRAK

Latar belakang. Ulkus kaki diabetik (UKD) adalah konsekuensi umum dan sangat tidak wajar dari diabetes yang sudah berlangsung lama dan yang tidak dikelola dengan baik. Studi kasus ini bertujuan untuk mengetahui efektivitas *Hydrogel-based wound dressings* (HBWD) dalam pengobatan UKD pada pasien diabetes.
Metode. Metode dalam studi kasus ini adalah laporan kasus berbasis bukti. Pertanyaan klinis yang digunakan: Apakah HBWD efektif dalam pengobatan UKD, terutama di fasilitas kesehatan dengan sumber daya terbatas? Untuk menjawab pertanyaan ini, kami mencari bukti dari *PubMed, Cochrane Database, Semantic Scholar, dan Google Scholar* dengan berbagai kata kunci berdasarkan pertanyaan klinis. Studi dipilih berdasarkan kriteria inklusi dan pengecualian yang telah ditentukan sebelumnya dan dinilai secara kritis.
Hasil. Empat uji coba terkontrol acak yang memenuhi kriteria inklusi dan pengecualian ditemukan. Tidak ada perbedaan yang signifikan dalam tingkat pengurangan area ulkus atau tingkat penutupan luka lengkap pada semua RCT. Jika dibandingkan dengan kelompok kontrol atau non-hidrogel, tiga penelitian melaporkan beberapa aspek yang menguntungkan pada kelompok HBWD, seperti

tanda-tanda inflamasi yang lebih sedikit dan tingkat penutupan luka lengkap yang lebih cepat sementara itu.
Kesimpulan. HBWD direkomendasikan dalam pengobatan UKD karena tersedia secara luas, hemat biaya, dan relatif mudah digunakan.

Keyword: *Hidrogel, Pembalut Luka, Ulkus Kaki Diabetik*

1. Introduction

Diabetic foot ulcers (DFUs) are a common and highly morbid consequence of long-standing and poorly managed diabetes. The incidence is up to 25% over a patient's lifetime. DFU and infection are the most common reasons for hospital admission [1]. The 5-year relative mortality after DFU is 48%, while other data suggest the mortality rate for people with DFU is 231 deaths per 1000 person-years, compared with 182 deaths per 1000 person-years in people with diabetes without DFU [1,2]. Approximately 20% of people who develop DFU will require lower-extremity amputation, either minor (below the ankle), major (above the ankle), or both [2], and 10% will die within 1 year of their first DFU diagnosis [3]. Both patient-specific factors (retinopathy, cardiovascular disease, kidney disease, smoking history, weight loss, inactivity) and foot-specific factors (prior ulceration, edema, callus, foot deformities) contribute to the risk of DFU [4].

The pathophysiology of DFU involves several components, and no one single component can contribute independently. These include metabolic causes, neuropathy, angiopathy, and changes in the immune system. The interaction between these components added together causes the development and progression of DFU [5,6].

Peripheral neuropathy, the most common intractable complication of diabetes, is responsible for more than 60% of DFUs. Peripheral neuropathy develops when the blood supply to peripheral nerves is insufficient, which in diabetes mostly occurs due to angiopathy. The automatic regulation of blood flow will be impaired and make peripheral nerves vulnerable to ischemia. Damaged nerve endings lead to pain perception due to disrupted action potentials, including hyperexcitability. It affects the sensory, motor, and autonomic nervous systems [6,7]. Peripheral neuropathy also gives rise to intrinsic muscle atrophy, consequently leading to biomechanical anatomical changes on the feet, such as hammer-toe formation, pes-planus, and pes-cavus, which eventually lead to high-pressure zones of the foot [8].

Sensory impairment due to peripheral neuropathy, along with neuronal autonomic dysfunction that can cause impaired sweat production and muscle wasting, are very important components in the pathophysiology of DFU. Other components, i.e. angiopathy and immune changes, also play crucial roles. The lack of protective sensation and anatomical changes in the feet predisposes patients with diabetes to develop trauma and ulcers [9,10].

The wound healing of DFU is a complex process that involves several overlapping phases, including inflammation, proliferation, and remodeling. Wound dressings play a crucial role in the management of DFU by creating a moist wound environment that promotes tissue regeneration, absorbs excess exudate, reduces inflammation, prevents infection, and protects the wound from further damage [11,12]. This leads to less pain, inflammation, necrosis, and scarring. Available dressings include hydrocolloids, hydrogels, films, and foams [13]. The advantages and disadvantages of each dressing are shown in Table 1.

Hydrogels are among the best materials for several biomedical applications. Polyvinyl pyrrolidone (PVP), a hydrogel polymer, has been used successfully as a basic material for the manufacturing of hydrogel wound dressings. It can absorb fluids, maintain a moist environment of the wound, and act as a barrier against microorganisms. However, one less desirable characteristic of hydrogels is their relatively poor mechanical strength [14]. The addition of agar as a second component is intended to enhance the mechanical strength of PVP-based hydrogel. However, the presence of agar may cause easier penetration of microorganisms into the hydrogel, particularly in a tropical environment where humidity is high. In this case, the addition of polyethylene glycol (PEG) improves the hydrogel barrier against microorganisms. The preparation involves a gamma ray irradiation technique. The resulting hydrogels show good biocompatibility, are widely applied, and are currently commercially available [15,16].

Table 1 Advantages and disadvantages of various wound dressings [17,18]

Dressing	Advantage(s)	Disadvantage(s)
Hydrocolloids	initially impermeable to water but progressively absorb water, becoming more permeable and forming a gel, lowering wound pH, inhibiting bacterial growth	can adhere to the wound and are hard to remove, unsuitable for necrotic or infected wounds, non-visual
Hydrogels	provide a moist environment, is comfortable, absorbent, integrated therapeutic substances, can be customized with a variety of polymers	non-visual, suitable only for minimal to moderate exudative wounds
Films	flexible, retains moisture, ability to monitor wounds visually, semi-permeable (allowing for gas exchange), self-adhesive	non-absorbent, impermeable to fluid, can cause maceration
Foams	absorb exudate, semi-occlusive, and semi-permeable, and their thickness allows for extra protection from external trauma	non-visual and inability to dry out a wound, some require a secondary film for adherence purposes

Hydrogel-based wound dressings (HBWD) have garnered increasing interest in the management of DFU due to their aforementioned excellent moisture-retaining properties and biocompatibility. In recent years, the anti-inflammatory function has also been added as a positive factor. HBWD are also relatively affordable, non-adherent, and provide a gentle and painless removal, reducing the risk of trauma to the wound bed. It can also be tailored to fit the size and shape of the wound. While HBWD has many benefits, they do have some limitations, such as the need for frequent changes, as they can become saturated with exudate, and the potential maceration of the surrounding skin [19,20].

Based on the enrichment biomaterial used, there are three types of HBWD composition: natural, synthetic, and hybrid polymers. Natural biomaterials such as chitosan, collagen, starch, cellulose, alginate, and hyaluronic acid are widely used. These natural polymers, which are formed from photosynthesis or a biochemical reaction in the natural world or extracted from natural products, show good degradability, biocompatibility, and nontoxic degradation products, and are in natural abundance. The disadvantages include low mechanical properties, high acquisition cost, small output, and difficult modification. Synthetic biomaterials such as polyvinyl alcohol, polyacrylamide, and PEG have good mechanical properties, large output, low cost, and rich variety. However, synthetic polymers often lack biological and biodegradable activity and may produce toxic by-products [21]. Hybrid hydrogel is made by combining natural and synthetic polymers. These hybrid hydrogel features improve formulations and versatile characteristics. Due to their versatility, this type of hydrogel has garnered increasing attention within the scientific community [22]. One of the common hybrid hydrogels is the alginate/PEG combination, first introduced in 1988. The molecular weight of the PEG molecule dramatically affected the mechanical properties of the cross-linked alginate gels, resulting in a relatively low number of free amino groups, indicating efficient cross-linking [23].

Despite its relatively affordable, easy-to-access, and easy-to-use nature, there is still a concern about the effectiveness of HBWD as a dressing of choice in the treatment of DFU compared with other types of dressing [24]. Hence, the clinical question: Does HBWD provide a satisfactory result in the treatment of DFU especially in limited-resource healthcare facilities? The aim of this evidence-based case report (EBCR) is to critically analyze whether the use of HBWD is effective compared to traditional dressing in the treatment of DFU and therefore to weigh the evidence for their daily clinical application. Assessment using the PICO (patient/population, intervention, comparison, outcomes) model is described in Table 2.

Table 2 PICO Assessment

Patient	Intervention	Comparison	Outcomes
Diabetic patients with diabetic foot ulcers	Hydrogel-based wound dressing	Traditional dressing or other non-hydrogel wound dressing	Reduction in ulcer area and/or improvements in infection and inflammation signs

Clinical Scenario

A 56-year-old woman with a 5-year history of type 2 diabetes mellitus (T2DM) came to the outpatient clinic with 12.0x6.8 cm and 3.5x2.0cm ulcers in her right calf for more than 3 months and numbness on both feet. Laboratory examination showed increased fasting and 2-hours postprandial blood glucose (141 mg/dl and 278 mg/dl, respectively), increased HbA1c (9.1%), and normal liver and renal function indexes. In the initial presentation, the diagnosis of DFU Wagner grade 3 and diabetic peripheral neuropathy was made. She has a history of poor glycemic control, is underweight, and comes from a low socio-economic household. There was also a previous history of DFU on her left foot. T2DM runs in the patient's family.

Since necrotic and infectious tissue were present, a simple debridement by removing the necrotic tissue and eschar was done. Drainage was performed and ecological soft tissue remained as much as possible. After debridement, the wound was cleaned with physiological saline and covered with a hydrogel dressing, personalized to fit the size and shape of the wound. We use a highly absorbent alginate-enriched HBWD for this patient (Dermafix Alginate Wound Dressing by OneMed®), composed of 100% calcium alginate [25]. The patient and her caregivers were asked to change the dressing every 3-4 days, depending on the amount of exudate and the presence of infection. To control the blood glucose, she has been given a basal-bolus insulin regimen along with a dietary plan. Other treatments include oral antibiotics, analgetic, neurotrophic agents, and antithrombotic agents. Biweekly control to the outpatient clinic was advised to monitor glycemic control and ulcer presentation.

After 4 months, there was a significant improvement in the patient's DFU. There was no necrotic and infectious tissue present and there was an increase in granulation formation (Figure 1). There was also a reduction in numbness symptoms, an increase in body weight, and better glycemic control. Bi- or triweekly control was then advised to the patient.

Figure 1 DFUs in baseline vs 4-months treatment with HBWD

2. Methods

A search of the literature was performed on May 1st and 2nd of 2024, using the keywords "diabetic foot ulcers", "diabetic wound", "hydrogel", and "treatment" along with its synonym and related terms, as shown in Table 3. The search was performed in 4 databases: PubMed, Cochrane Database, Semantic Scholar, and Google Scholar. Inclusion criteria are any articles that were clinical trials, systematic reviews, or meta-analyses that focused on the role of HBWD in the management of DFU. Exclusion criteria are articles that were reviewed, case reports, and guidelines. We limit the search to articles published in the last 10 years.

The primary selection was based solely on the title and abstract using inclusion and exclusion criteria as mentioned earlier. After the primary election, the next selection includes reading the full article and filtering which article is suitable for the analysis. We also searched for references in the articles that matched the inclusion and exclusion criteria, that were not included in the databases. The search strategy and results are shown in Figure 2. After the selection, critical appraisal was done using several aspects based on the Center of Evidence-based Medicine, University of Oxford for therapy study [26].

Table 3 The search strategy used in 4 databases

Database	Search strategy	Results
PubMed (May 1st, 2024)	(((((((diabetic ulcer [MeSH Terms] OR (diabetic wound [MeSH Terms]))) AND (treatment [Title/Abstract])) OR (management [Title/Abstract])) AND (hydrogel [Title/Abstract])	1252
Cochrane Database (May 1st, 2024)	"diabetic ulcer" in Title Abstract Keyword OR "diabetic wound" in Title Abstract Keyword AND "management" in Title Abstract Keyword OR "treatment" in Title Abstract Keyword AND "hydrogel" in Title Abstract Keyword	4916
Google Scholar (May 2nd, 2024)	Allintitle: diabetic ulcer hydrogel	8
	Allintitle: diabetic wound hydrogel	43
Semantic Scholar (May 2nd, 2024)	hydrogel; diabetic ulcer + filters	505
	hydrogel; diabetic wound + filters	295

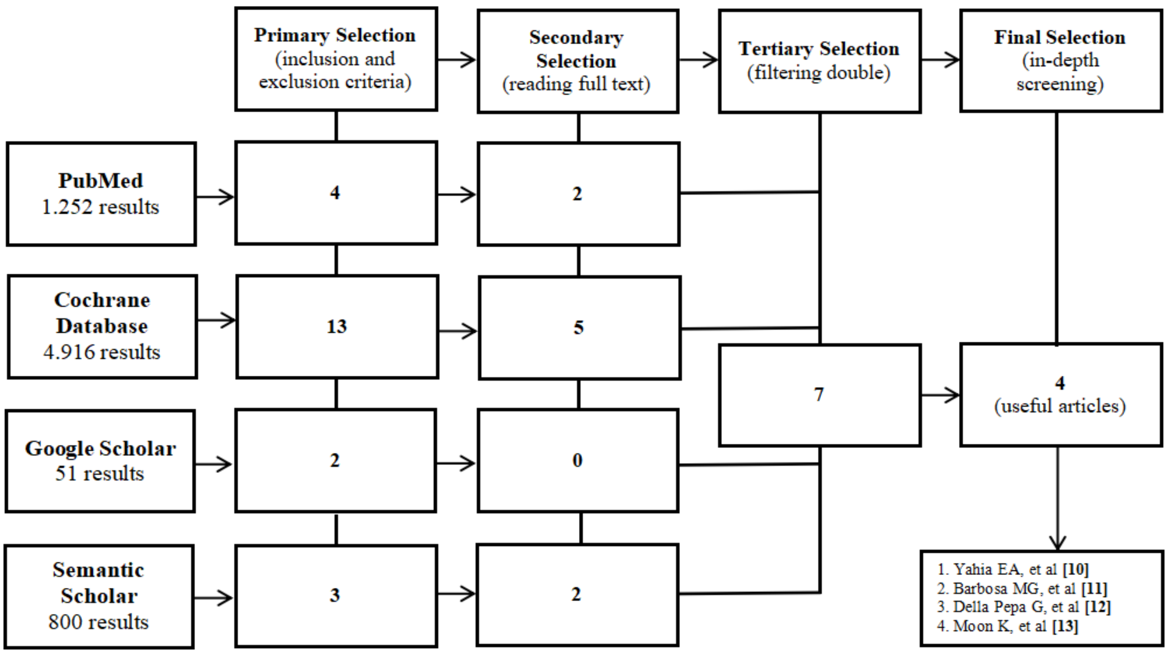

Figure 2 Flowchart of search strategy

3. Results

Based on this search strategy, we found 4 original articles, all of which were a randomized controlled trial (RCT) [27-30] The design and summary of the result are available in Table 4. The critical appraisal is shown in Table 5. All RCTs were considered to have good validity, although there were some limitations. A total of 162 participants were enrolled in the studies. The first three articles were single-center and non-blind studies [27-29]. While the last article from Moon K, et al was a multicenter and single-blind study [30].

Table 4 Design and summary of results from the selected articles

Article	Method	n	Comparison	Hydrogel enrichment	Primary outcome	Secondary outcome
Yahia et al., Cairo (Egypt), single center, 2021	RCT	60	Hydrogel dressing vs traditional dressing	Nanosilver	RUA 75.56% vs 65.17%, p=0.712 (W3)	No data
Barbosa et al., Sao Paulo (Brazil), Single Center, 2022	RCT	26	Hydrogel dressing vs control	Sodium alginate, vitamins A and E	RUA 55.97% (20.59-95.09%) vs 6.12% (0-69.35%), p=0.418 (W12)	Microscopic evaluation: The hydrogel group has significantly lower inflammatory infiltrates than the control group (W12)
Della Pepa et al., Naples (Italy), single center, 2023	RCT	37	Hydrogel dressing vs saline gauze	*Triticum vulgare* extract and Polyhexanide	RUA -2.7±1.7 cm vs -3.9±1.9 cm, p=0.300 (W12)	Reduction in a score of erythema, edema, and dry skin: hydrogel vs saline group W3, W4, W5: p=0.021*, p<0.001*, p=0.04*, respectively
Moon et al., Seoul (South Korea), multi-center, 2019	RCT	39	Hydrogel dressing vs control	Allogeneic adipose-derived stem cell	CWC 73% vs 47%, p=0.102 (W8), CWC 82% vs 53%, p=0.053 (W12)	CWC mean time ASC vs control group: 40.8±5.3 days vs 51.2±3.9 days, p=0.033*

RCT: randomized control trial, RUA: reduction of ulcer area, CWC: complete wound closure, ASC: allogeneic adipose-derived stem cell, n: study participants, W: week,
*p<0.05 considered significant

Although HBWD is considered a good option in the treatment of DFU, surprisingly none of the studies showed a clear benefit of HBWD therapy. A study by Yahia EA, et al showed there was a higher rate of reduction of ulcer area (RUA) in 30 patients receiving nanosilver-enriched HBWD compared to 30 patients receiving traditional dressing (i.e clean linen gauze), although it was statistically insignificant [27]. Similarly, Barbosa MG, et al showed no significance in RUA after 12 weeks in the hydrogel group compared to the control group, although they do claim there were significantly lower inflammatory infiltrates based on histological examinations in the hydrogel group [28].

Promising results of HBWD therapy in DFU come from the study by Della Pepa G, et al. Although they showed no difference in RUA after 12 weeks in patients receiving *Triticum vulgare* extract and polyhexanide-enriched hydrogel compared to the saline gauze group, they reported that there was a significant reduction in score of erythema, edema, and dry skin from 3rd to 5th week of treatment in the hydrogel. This in turn will result in less pain and more comfort for patients [29].

Table 5 Critical appraisal of the articles

Articles		Yahia et al. [10]	Barbosa et al. [11]	Della Pepa et al. [12]	Moon et al. [13]
Validity	Was the assignment of patients to treatment randomized?	Yes	Yes	Yes	Yes
	Were the group similar at the start of the trial?	NS	NS	Yes	Yes
	Aside from the allocated treatment, were groups treated equally?	Yes	Yes	Yes	Yes
	Were all patients who entered the trial accounted for? And were they analyzed in the groups of which they were randomized?	LoF 0% Yes	LoF 26.92% Yes	LoF 7.5% Yes	LoF 0.18% Yes

	Were measures objectives or were the patients and clinicians kept "blind" to which treatment was being received?	No	No	No	Single blind
Importance	How large was the treatment effect?	RUA 75.56% vs 65.17% (week 3)	RUA 55.97% vs 6.12% (week 12)	RUA -2.7cm vs -3.9cm (week 12)	CWC 82% vs 53% (week 12)
	How precise was the estimate of the treatment effect?	NS	NS	NS	NS
Applicability	Is my patient so different from those in the study that the result cannot apply?	No	No	No	No
	Is the treatment feasible in my setting?	Yes	Yes	No	No
	Will the potential benefit of the treatment outweigh the potential harm of treatment for my patient?	Yes	Yes	Yes	Yes

NS: not specified, LoF: loss of follow-up, RUA: reduction of ulcer area, CWC: complete wound closure

The last study by Moon K, et al primarily evaluate the complete wound closure (CWC) of DFU. There was no significant difference in CWC rate from the allogeneic adipose-derived stem cell (ASC)-enriched hydrogel compared to the control group. They, however, reported there was a significantly faster mean CWC time in the experimental group [30].

4. Discussions

All studies fail to show the superiority of HBWD therapy in terms of RUA or CWC in DFU patients. This is probably because low number of participants and the relatively short duration of treatments. Two studies (Yahia EA, et al and Barbosa MG, et al) also lack similar baseline characteristics in both experimental and control groups. This finding differs from that of another study [27,28]. A meta-analysis study of 15 RCTs with 872 eligible patients comparing hydrogel dressing with conventional dressing, showed significant improvement in healing rate, shortened healing time, enhanced granulation formation and epithelial formation, and reduced the incidence of bacterial infection, all favoring the hydrogel group [31].

Natural polymers are the basis for obtaining HBWD with great potential. Alginate cross-linked with copper ion, in particular, due to its increased hydrophilicity, can absorb the exudate of a wound and keep it moist. Alginate also useful as is a release platform for controlled-release therapeutic substances (i.e. antibacterial and anti-inflammatory agents). Compared to other enrichments, alginate has a better absorbent feature [32-34]. Our patient, along with the study from Barbosa et al, used alginate-enriched HBWD with positive results. Although no RUA or CWC was observed in our patient, there was no necrotic and infectious tissue present, there was an increase in granulation formation, and better glycemic control after 4 months of treatment.

Additionally, the studies show another benefit of HBWD therapy. Two of the studies (Barbosa MG, et al and Della Pepa G., et al), reported fewer inflammatory signs in the hydrogel group compared to the non-hydrogel group. These findings are based on histological and clinical scores, respectively [28,29]. Hydrogel dressing potential to assist wound healing, including during the inflammatory process, has been investigated since the 1980s. The hydrogels will absorb the wound exudate and maintain it away from the wound bed [35].

Another great advantage of HBWD is that its intrinsic properties can be improved by adding active compounds, such as antibiotics, nanoparticles, stem cells, and growth factors. For instance, ionic silver-enriched hydrogel dressing has been proposed in several wound care products as an efficient antimicrobial to be used against pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* [36]. All 4 RCTs in this EBCR article used different enrichment in their respective studies: nanosilver, sodium alginate, vitamins A and E, *Triticum vulgare* extract and polyhexanide, and ASC [27-30]. Other enrichments or active compounds that can be used for HBWD are polyphenols, copper, ZnO nanoparticles, and nitrofurazone [35].

As mentioned earlier, hydrogels can be used for the delivery of stem cells to the wound site. They are an attractive alternative to conveyance vehicles, as they increment the period that stem cells live at a wound site. This property emerges from the capacity of certain hydrogels to elevate cell bonds and to engage stem cell activity by supporting the upkeep of their ordinary aggregate [37]. One of the studies included in this EBCR also used stem cell-based enrichment with promising results [30].

Lastly, the cost-effectiveness of HBWD is still a main concern, especially in patients with low socio-economic backgrounds [38]. Although all of the studies in the selected articles did not mention the cost-effectiveness or economic benefits of each group, it is worth noting that currently, HBWD is one of the most commercially available dressings in the market [39]. One study revealed that hydrogel dressing significantly has a lower overall cost than normal saline gauze dressing in the treatment of DFU and perioperative wound dehiscence [40]. One review article also mentioned the cost-effectiveness of HBWD compared to traditional and cheaper dressing in various types of wounds [41]. Another article proposed cost-effective antimicrobial HBWD for modern wound dressings [42].

5. Conclusions

In conclusion, HBWD can be recommended in the treatment of DFU. It is widely available, cost-effective, and relatively easy to use both in the household and the outpatient clinic. Although some downsides persist, such as maceration in the surrounding skin and the need for frequent changes, its ability to maintain a moist environment is essential for optimal wound healing. In this EBCR, we have shown that by adding active compounds, the hydrogel dressing ability can be enhanced even more. Therefore, there is still room for improvements in HBWD, such as the exploration of new hydrogel material or the development of smart hydrogel dressing that is capable of sensing changes in the wound environment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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