Human-derived Acellular Dermal Matrix Grafts for Treatment of Diabetic Foot Ulcers: A Systematic Review and Meta-analysis

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ABSTRACT

Background. Treating diabetic foot ulcers (DFUs) requires thorough understanding of available surgical tools. **Objective.** This meta-analysis compares human-derived acellular dermal matrices (H-ADMs) with standard of care (SOC) to evaluate the number of healed ulcers at 12 and 16 weeks and number of days to complete healing. As a secondary outcome, the efficacy of 3 H-ADM subtypes are studied. **Methods.** Two researchers searched PubMed, EMBASE, and The Cochrane Central Register of Controlled Trials for relevant titles from inception through July 2018. Inclusion criteria indicated articles be randomized controlled trials investigating the effects on neuropathic, nonischemic DFUs. **Results.** Data from 312 DFUs in total were included in the meta-analysis. The results show H-ADMs are more effective in healing patients within a 12-week (3.14; range, 2.04–4.83) and 16-week period (2.35; range, 1.25–4.43) in comparison with SOC. Further, the mean time to complete healing was shorter in the H-ADM group (-2.31 days; range, -2.67 to -1.95 days) in comparison with SOC. Within the subgroups, 2 H-ADMs were associated with a higher likelihood of complete healing within 12 weeks when compared with SOC. The third H-ADM had a point estimate, which suggested superiority over SOC. **Conclusions.** This study shows H-ADMs are associated with a higher likelihood of complete healing and fewer days to complete healing within a 12-week and 16-week periods when compared with SOC. Also, the commercial products performed similarly.

KEY WORDS

diabetic foot ulcer, acellular dermal matrix, biologics, wound healing, standard of care, human-derived acellular dermal matrix, meta-analysis

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Foot wounds are a common complication associated with diabetes mellitus (DM) and often impose significant economic, health, and quality of life burdens upon patients and health care systems. Diabetes affects more than 22 million people in the United States.[1] Up to 25% of these people are at risk for developing a diabetic foot ulcer (DFU), with an annual prevalence estimated at 13%.[1,2] Armstrong et al[3] posit nearly 40% of people with a DFU experience a recurrence within 1 year from healing. Substantial prevalence paired with a high rate of DFU recurrence leads to high expenditure of health care dollars. In a 2014 study by Rice et al,[4] the results suggest an annual incremental payer burden of up to $13.2 billion in the United States alone. In addition, DFUs can cause enormous personal hardships to patients, such as higher rates of depression, lack of mobility, and increased tensions with caregivers.[5] Thus, it remains an important public health initiative to treat these wounds quickly and effectively.

Treatment of DFUs focuses on pressure offloading, local wound care (standard of care [SOC]), infection control, and surgical intervention when necessary. Peripheral neuropathy commonly associated with DM decreases protective sensation of the foot. Repetitive stress, trauma, or shear forces lead to skin breakdown. Peripheral vascular disease can lead to ischemia of the distal lower extremity, which compromises native wound healing ability. The Wound Healing Society (WHS) 2013 DFU treatment guidelines[1] promote pressure offloading, reduction of bacterial and cellular burden through adequate debridement, local wound care with moist dressings that also absorb wound exudate, topical and systemic antibiotic therapy when needed, and treatment of osteomyelitis. Further, the guidelines[1] state cellular and acellular equivalents improve DFU healing by releasing growth factors, cytokines, and proteins that stimulate the wound bed. Human-derived acellular dermal matrix (H-ADM) products consist of cadaveric skin processed to remove antigenic cells while retaining the dermal extracellular matrix crucial for angiogenesis and structural support of collagen.[6]

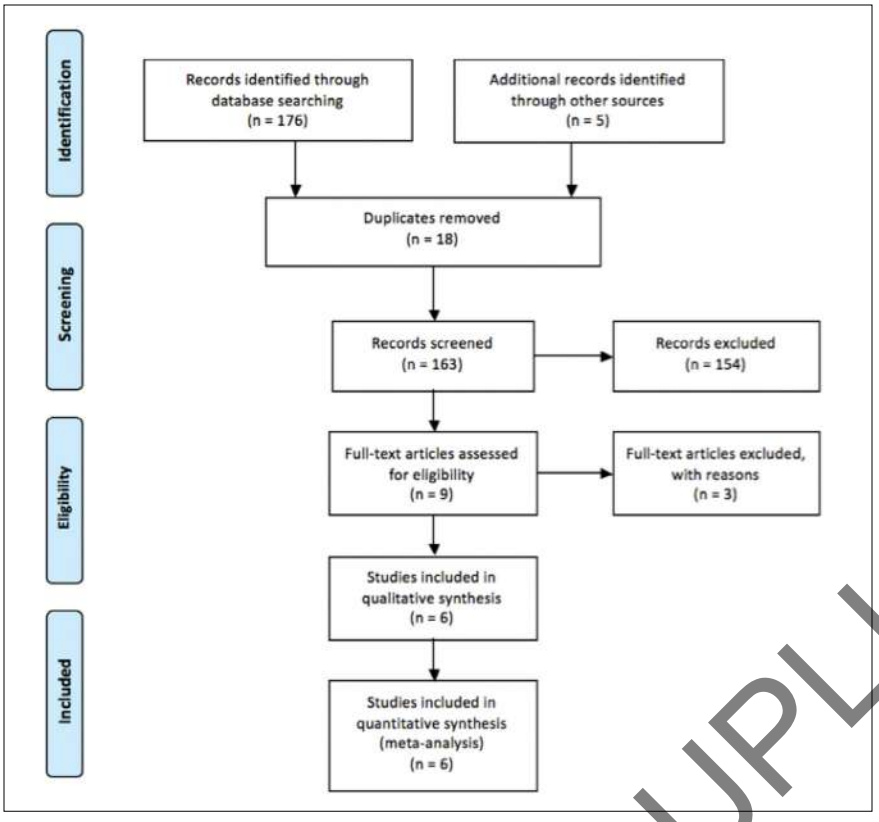

Figure 1. Literature search flow diagram.

Table 1. Inclusion criteria

Clinical human study
Prospective, randomized, controlled trial
Patients with diabetes mellitus type 1 or 2
Patients >18 years old
Neuropathic, nonischemic diabetic wounds of the foot investigated
Use of a human-derived acellular dermal matrix

Table 2. Exclusion criteria

Nonprospective study
Study design other than randomized controlled trial
No comparison between human-derived acellular dermal matrix and control
Animal-derived or synthetic acellular dermal matrix

This study aimed to provide an updated search of the literature examining local wound care versus treatment with an H-ADM for neuropathic, nonischemic DFUs. A complete meta-analysis comparing superiority of SOC versus H-ADM use, focusing on the number of wounds healed at 12 and 16 weeks of treatment and number of days to complete healing, was conducted. Also, a subgroup analysis comparing the 3 individual H-ADMs was performed.

METHODS

Studied H-ADMs

The studies included in this meta-analysis investigated 3 subtypes of H-ADM: AlloPatch Pliable (H-ADM Product A; MTF Biologics, Edison, NJ), DermACELL (H-ADM Product B; Stryker, Kalamazoo, MI), and GRAFTJACKET (H-ADM Product C; Wright Medical Group, Memphis, TN). These 3 H-ADM subtypes were chosen for analysis among other commercially available H-ADMs solely based on their mention in published studies that met inclusion criteria. The H-ADMs differ in the proprietary processing of the human-derived donor skin.

Data sources and searches

Two researchers (M.L. and T.M.) independently searched PubMed, EMBASE, and The Cochrane Central Register of Controlled Trials for relevant titles from inception through July 2018. A diagram of the search process is presented in **Figure 1**. The following combinations of search terms were employed: "Diabetic foot, Foot Ulcer, Acellular Dermis," "Diabetic Foot Ulcer, Acellular," "Acellular Dermis," and "Acellular Matrix, Diabetic." The combinations returned 176 titles. Reference lists also were searched, yielding an additional 5 relevant titles. After removing 18 duplicates, 163 abstracts were screened for inclusion, using the criteria detailed in **Tables 1** and **2**. The researchers performed full-text analysis of 9 articles for eligibility, 3 of which were excluded due to lack of outcomes data necessary for the meta-analysis. Only randomized controlled trials (RCTs) were considered for inclusion, so as to obtain the highest level of evidence possible for meta-analysis. In addition, only English-language articles were considered.

Data extraction

All included articles focused on neuropathic, nonischemic DFUs treated with debridement and placement of H-ADMs versus debridement and SOC. Independently, 2 separate researchers (M.L. and T.M.) extracted data directly from each study using a standardized form. Data were reported as the number of events or converted into mean plus or minus standard deviation where applicable, as suggested by the Cochrane handbook.[7] In this review, an *event* refers to complete healing of a wound by the original study authors; events were compared using odds ratios (ORs). The *means* in this review refer to the number of days to complete healing and were compared using a mean and standard deviation. A majority of the studies assessed included 1 or both of these values and thus allowed for direct

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Table 3. Characteristics of included studies

STUDY (y)	NO. PATIENTS	TREATMENT	MEAN WOUND SIZE (cm²)	MEAN AGE (y)	MEAN BMI
Zelen et al[12]; 2018	40	H-ADM Product A [a]	3.2	59	35
	40	SOC	2.7	62	34
Zelen et al[13]; 2017	20	H-ADM Product A	4.7	61.5	33.9
	20	SOC	2.7	57.1	32.3
Cazzell et al[10]; 2017	53	H-ADM Product B [b]	3.9	59.1	32.56
	23	H-ADM Product C [c]	3.3	58.5	31.41
	56	SOC	3.6	56.9	32.82
Walters et al[9]; 2016	53	H-ADM Product B	3.6	58	31.2
	23	H-ADM Product C	3.3	58.7	31.7
	56	SOC	3.1	57.1	32.9
Reyzelman et al[14]; 2009	46	H-ADM Product C	3.6	32	39.9
	39	SOC	5.1	18	47.6
Brigido[11]; 2006	14	H-ADM Product C		61.43	
	14	SOC		66.21	

y: year; BMI: body mass index; H-ADM: human-derived acellular dermal matrix; SOC: standard of care

[a] AlloPatch Pliable (MTF Biologics, Edison, NJ)

[b] DermACELL (Stryker, Kalamazoo, MI)

[c] GRAFTJACKET (Wright Medical Group, Memphis, TN)

comparison. Researchers were not blinded to the study being investigated, as the literature has shown blinding to have no significant bearing on meta-analysis outcomes.[8] Studies conducted by Walters et al[9] and Cazzell et al[10] were noted to have utilized common data. Consequently, the results from these articles were pooled so as to not overestimate the weight of effect from a shared dataset.

Brigido[11] presented the results for percentage of wounds completely healed as a receiver operating characteristic curve. The authors used n-values for H-ADM Product C and SOC groups in the position of that graph to calculate the number of complete healing events. In the present study, the authors compared these data points to that from other included studies[9-14] to calculate ORs.

Statistical analysis

This meta-analysis was completed using RevMan Version 5.3 (Cochrane Community; Copenhagen, Denmark). Mean difference with 95% confidence intervals (CIs) was calculated for continuous data and ORs with 95% CIs calculated for the dichotomous data. Statistical significance was set at $P < .05$. The calculations revealed significant heterogeneity between studies with $I^2 > 50\%$, where applicable, prompting use of a random effects model for analysis. As such, weights were assigned in the final meta-analyses based on effect size.

RESULTS

There were 6 identified studies[9-14] that compared the use of H-ADMs with SOC for the treatment of DFUs. The included studies focus on the number of completely healed wounds over 12 weeks and mean time (in days) to complete wound healing as primary outcomes. Current SOC generally was defined as debridement of wounds as necessary and coverage with an absorbent, dry dressing. **Table 3**[9-14] presents the characteristics of the included studies.

Included studies

Zelen et al.[12] The authors of this study conducted a prospective RCT at 5 wound care centers across the United States. The study population was divided into 2 groups for comparison. The first group was treated with human-reticular acellular dermal matrix (HR-ADM; H-ADM Product A) plus SOC. The second comparison group was treated with SOC alone. Standard of care consisted of sharp debridement, daily dressing changes with a collagen alginate (FIBRACOL Plus Collagen Wound Dressing; KCI, San Antonio, TX), followed by a 3-layer, padded, generic dressing of gauze, soft roll, and a compressive wrap. Offloading was performed using a removable cast walker (Royce Medical Company Inc, Los Angeles, CA). Wounds were measured using acetate tracing. A total of 80 patients with DFUs (University of Texas Grade 1 or 2) larger than 1 cm² and located below the malleoli were randomized into the 2 treatment groups. The primary outcome was measured as wounds closed at 6 weeks. A hydrogel bolster was used after weekly HR-ADM application. In the HR-ADM group, 68% were completely healed at 6 weeks compared with 15% in the SOC group. The proportion of wounds healed at 12 weeks was 80% and 30%, respectively. The mean time to heal within 12 weeks was 38 days for the HR-ADM group and 72 days for the SOC group. Zelen et al concluded HR-ADM is clinically superior to SOC, cost effective in relation to other comparable treatment modalities, and an efficacious treatment for chronic, nonhealing DFUs.

Zelen et al.[13] This prospective RCT compared the clinical outcomes of a HR-ADM (H-ADM Product A) to facilitate wound closure in nonhealing DFUs as compared with SOC. Standard of care was described as sharp debridement and dressings with collagen alginate and gauze. All wounds were treated with offloading using a total contact cast (TCC) and removable walker. Surface area of the wounds was calculated and measured from an acetate sheet tracing. No location or grading system was used to characterize the wounds in this study. Patients were randomized to either

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SOC alone or HR-ADM plus SOC applied weekly for up to 12 weeks. Patients with HR-ADM placement had the graft covered with a nonadherent dressing (ADAPTIC TOUCH Non-Adhering Silicone Dressing; KCI), followed by a moisture-retentive dressing (hydrogel bolster) and a padded 3-layer dressing (DYNA-FLEX Multi-Layer Compression System; KCI). Of the HR-ADM-treated wounds, 80% (16/20) had healed compared with 20% (4/20) of the wounds that received SOC alone (P = .00036). Mean time to heal within 12 weeks was 40 days (95% CI, 27–52 days) for the HR-ADM group compared with 77 days (95% CI, 70–84 days) for the SOC group (P = .00014). The authors concluded that a weekly application of HR-ADM was an effective intervention for promoting closure of nonhealing DFUs.

Cazzell et al.[10] This study consisted of a prospective RCT to compare the DFU treatment efficacy and safety of an acellular dermal matrix (H-ADM Product B) with (1) a conventional care arm and (2) a previously studied human-derived acellular dermis comparator (H-ADM Product C). In this study, SOC was described as sharp debridement with a blade, scissors, or hydrosurgery (VERSAJET II Hydrosurgery System; Smith & Nephew, Fort Worth, TX). Moist wound treatments using alginate, foam, or hydrogel dressings were common SOC adjuncts. Offloading of all wounds was performed with a removable cast walker, diabetic shoe, surgical shoe, walker cast, or TCC. In total, 168 Wagner DFU Grade 1 or 2 ulcers between 1 cm^2 and 25 cm^2 were evaluated. These wounds were managed with SOC for 30 days. Location of the wound was not specified in this study. Measurement was performed using 3D wound imaging (Silhouette; ARANZ Medical Ltd, Christchurch, New Zealand). Subjects were followed for 24 weeks. Single application of H-ADM Product B demonstrated significantly greater average percent wound area reduction than SOC at 12 weeks (65.0% vs. 41.1%, P = .0123), 16 weeks (82.5% vs 48.1%, P = .0003), and 24 weeks (89.7% vs. 67.3%, P = .008), respectively.

Single application of H-ADM Product C showed significantly greater wound area reduction over SOC for weeks 4 to 6, 9, 11, and 12. Also, H-ADM Product B demonstrated significantly greater wound healing, larger wound area reduction, and a better capability of keeping healed wounds closed compared with SOC in the treatment of chronic DFUs.

Walters et al.[9] This multicenter RCT assessed the healed ulcer rate of H-ADM Product B compared with SOC and H-ADM Product C in the treatment of full-thickness DFUs. Wounds were described as single, full-thickness target DFUs with a Wagner DFU Grade 1 or 2. Wounds with an area of 1 cm^2 to 25 cm^2 and a depth of 9 mm or less were included in the analysis. Detailed location of the wounds was not specified in this study. Standard of care was described as sharp debridement, advanced moist wound therapy with alginates, and use of foams or hydrogels. Patients in all groups underwent offloading therapy with a removable cast walker, diabetic shoe, surgical shoe, walker cast, or TCC. Prior to interventions, wounds were measured and recorded using 3D wound imaging (ARANZ Medical Ltd). In total, 168 patients were randomized into H-ADM Product B, SOC, and H-ADM Product C treatment arms in a 2:2:1 ratio. Treatment groups underwent application of the different H-ADMs after wound preparation and subsequently were covered with an appropriate nonadherent dressing, including oil emulsion dressings or hydrogel. Bolstering of the H-ADM was left at the discretion of the treating physician. Negative pressure wound therapy also was permitted but not used on all patients. A second application of H-ADM was performed on some patients (13 patients received 2 applications of H-ADM Product B and 7 patients received 2 applications of H-ADM Product C), as deemed necessary by the treating physicians. Weekly follow-up visits were conducted until the ulcers healed completely or the endpoint was reached. The H-ADM Product B group had a significantly higher proportion of completely healed ulcers than the SOC group (67.9% vs. 48.1%, P = .0385, respectively) and an insignificantly higher proportion than the H-ADM Product C group (67.9% vs. 47.8%, respectively). The results presented support H-ADM Product B as an appropriate clinical option in the treatment of DFUs, with significant increases in healing rates and rate of percentage wound closure as compared with SOC options.

Reyzelman et al.[14] This article details a prospective, multicenter RCT that compared the proportion of healed DFUs and mean healing time between patients receiving H-ADM Product C (study group) and SOC therapies (control group). The SOC was defined as surgical debridement, moist wound therapy with alginates, foams, hydrocolloids, or hydrogels at the discretion of the treating physician. In addition, both groups were treated with offloading performed using a removable cast walker (Royce Medical, Inc). Patients in this study had University of Texas Grade 1 or 2 DFUs ranging from 1 cm^2 to 25 cm^2. In total, 86 subjects were randomized into the H-ADM Product C group (n = 47) and the control group (n = 39). Single application of H-ADM Product C was used, followed by a silver-based nonadherent dressing placement. The difference in proportion of healed ulcers between groups was statistically significant, with complete healing of 69.9% in the study group and 46.2% in the control group (P = .0289). After adjusting for ulcer size at presentation (a statistically significant covariate [P = .0194]), odds of healing were shown to be 2 times higher in the study group versus control group (P = .0233). This study supports the use of single-application H-ADM Product C as an effective treatment of DFUs.

Brigido.[11] The author of this study performed a prospective RCT to determine the efficacy of H-ADM Product C (study group) in wound repair compared with SOC (control group) for chronic, nonhealing, full-thickness wounds of the lower extremity secondary to diabetes. The population studied was a cohort of 40 patients with chronic wounds of the legs or feet lasting more than 6 weeks. Wound location was not specified, and no ulcer classification system was used in this study. Patients

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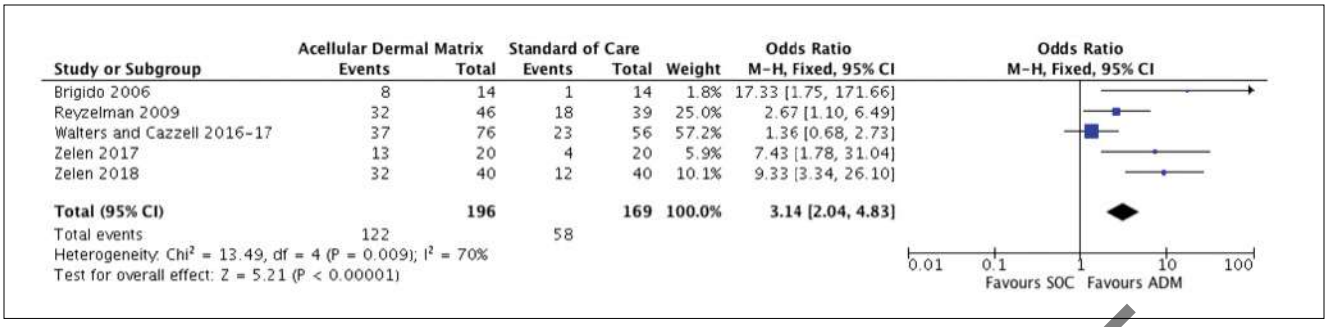

Figure 2. Forest plot of complete healing at 12 weeks between H-ADM and SOC.
H-ADM: human-derived acellular dermal matrix; SOC: standard of care; CI: confidence interval; df: degrees of freedom

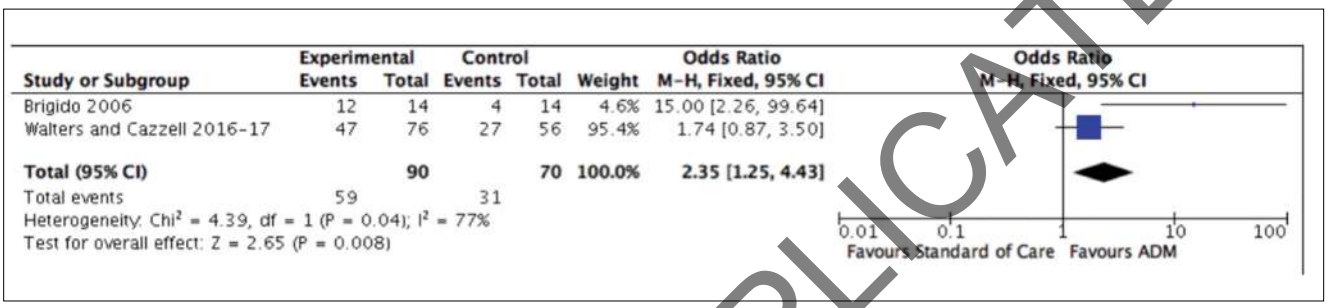

Figure 3. Forest plot of complete wound healing at 16 weeks between H-ADM and SOC.
H-ADM: human-derived acellular dermal matrix; SOC: standard of care; CI: confidence interval; df: degrees of freedom

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were randomly assigned to the study or control group. Standard of care in the control group included sharp debridement, CURASOL Gel Wound Dressing (Smith & Nephew) with gauze dressings, and offloading. Patients in the study group received a single application of H-ADM Product C with a mineral oil-soaked fluff compressive dressing to maintain a moist environment, in addition to offloading treatment. Patients in both groups were assessed weekly for 4 weeks. Wounds were measured using wound tracing on wound film. After 4 weeks of follow-up, the study group showed a statistically significant decrease in wound area by 67.4% compared with 34% reduction in wound area from the control group. The trial concluded at 16 weeks; data at that point revealed 85.7% of the wounds in the study group had completely healed, while only 28.5% of the wounds in the control group had fully healed ($P = .006$). The average time to heal in the study group was 11.9 weeks and 13.5 weeks in the control group. The authors concluded that there is a significant increase in wound healing rate with the use of H-ADM Product C when compared with SOC.

Meta-analysis: complete wound healing at 12 weeks

A forest plot comparing complete wound healing at 12 weeks for DFUs treated with H-ADMs against those treated with SOC is shown in **Figure 2**.[9-14] An event represents a completely healed wound. In total, 312 DFUs are represented from the 6 included studies.

The meta-analysis suggests overall superiority of DFU treatment with H-ADMs over SOC at the 12-week follow-up. Wounds treated with H-ADMs, overall, were nearly 3.14 times more likely to have shown complete healing at 12 weeks when compared with SOC treatment alone (OR, 3.14; 95% CI, 2.04–4.83; $P = .01 \times 10^{-3}$). Of note, the combined data from Walters et al[9] and Cazzell et al[10] showed an OR that was not significantly different from SOC. The CI crossed the line of no effect, rendering these data inconclusive in isolation.

Meta-analysis: complete wound healing at 16 weeks

In **Figure 3**,[9-11] a forest plot shows a comparison of complete wound healing at 16 weeks for DFUs treated with H-ADM versus those treated with SOC. A total of 160 ulcers were included in this analysis. Of note, 3 studies with 2 separate datasets included results from this extended timeframe. The results suggest H-ADM superiority over SOC at 16 weeks, with an OR of 2.35 favoring the treatment arm (95% CI, 1.25–4.43; $P = .008$).

Meta-analysis: time to complete healing

Only 3 studies[12-14] meeting inclusion criteria contained the necessary data for mean days to complete healing analysis (**Figure 4**[12-14]). The heterogeneity between these studies was high ($I^2 = 77\%$); thus, a random effects model was employed. Results show superiority of H-ADM over SOC, with a mean standard effect suggesting fewer average days to complete healing associated with use of H-ADM over SOC.

Sub-analysis: H-ADM subtype healing at 12 weeks

The forest plot evaluating complete DFU healing at 12 weeks for specific H-ADMs versus SOC is provided in **Figure 5**.[9-12,14] The H-ADMs were subgrouped into 3 categories based on the

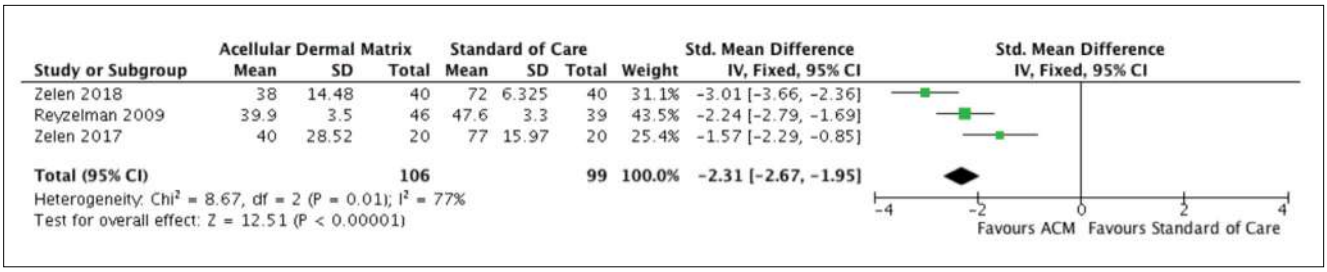

Figure 4. Forest plot of time to complete healing between H-ADM and SOC.
H-ADM: human-derived acellular dermal matrix; SOC: standard of care; CI: confidence interval; Std: standard; SD: standard deviation; df: degrees of freedom

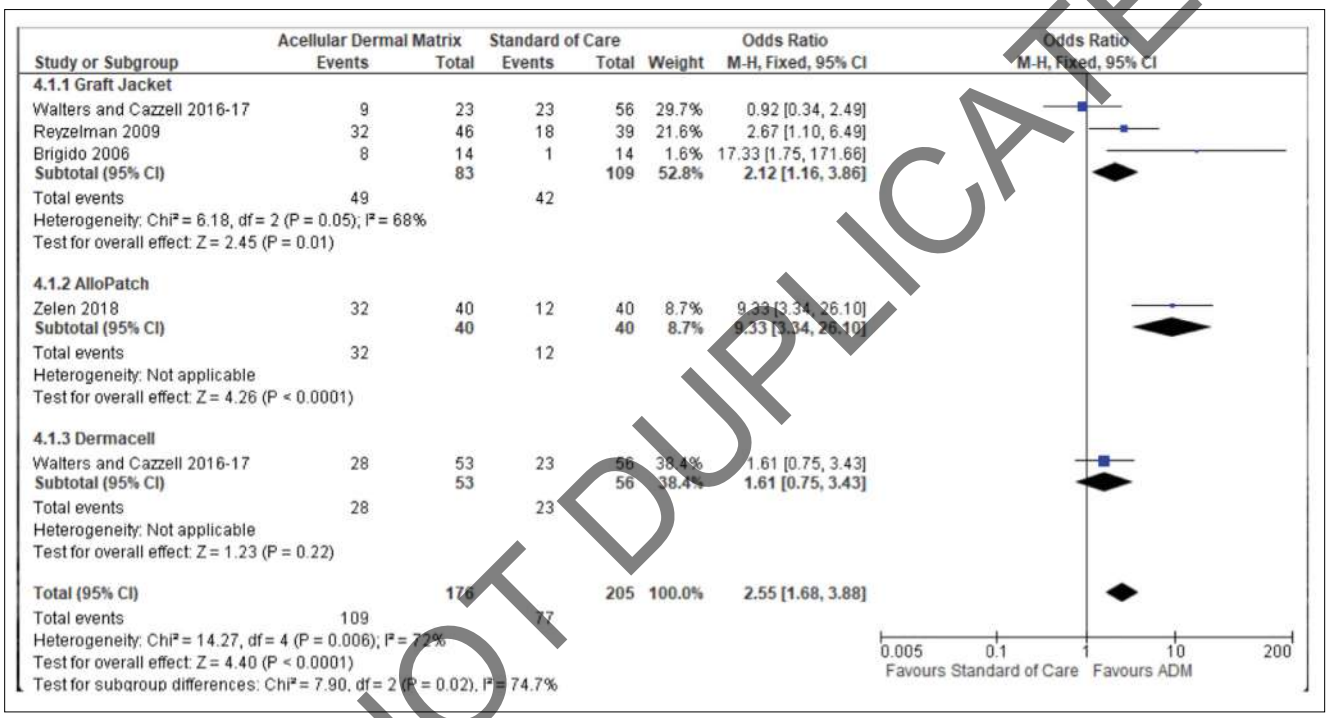

Figure 5. Time to complete healing at 12 weeks, grouped H-ADM vs. SOC.
H-ADM: human-derived acellular dermal matrix; SOC: standard of care; CI: confidence interval; df: degrees of freedom

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3 products utilized in the included studies (H-ADM Product A, H-ADM Product B, and H-ADM Product C). Per the data, H-ADM Product C and H-ADM Product A subgroups were 2.12 times (95% CI, 1.16–3.86; Z = 2.45; *P* = .01) and 9.33 times (95% CI, 3.34–26.10; Z = 4.26; *P* < .0001) more likely to show complete DFU healing at 12 weeks than SOC, respectively. The H-ADM Product B subtype failed to demonstrate statistically significant superiority over SOC, with a CI including the null 1.0 (1.61; 95% CI, 0.75–3.43). The Cazzell et al[10] and Walters et al[9] studies both individually stated significant superiority of H-ADM Product B over SOC at 12-week and 16-week follow-up. When these data were pooled into the forest plot (**Figure 5**[9-12,14]), the CI crossed the line of no effect. Although the point estimate suggests a trend toward H-ADM Product B superiority, the data are insignificant in this context. When comparing between subtypes, tests for heterogeneity were statistically significant (χ^2 = 14.27; degrees of freedom [df] = 4; *P* = .006; I^2 = 72%; α = 0.05). This suggests, despite all the groups being statistically different from SOC treatment with 95% confidence, the effects noticed were not similar to the same degree of confidence. A test for subgroup differences showed statistically significant differences between brands (χ^2 = 7.90; df = 2; *P* = .02; I^2 = 74.7%). The H-ADM Product A significantly demonstrated the most superiority of the 3 H-ADM groups for the number of wounds healed at 12 weeks when compared with SOC.

Sub-analysis: average time to complete healing by H-ADM subtype

A forest plot comparing ORs for mean time to complete DFU healing between H-ADM subtypes versus SOC is provided in **Figure 6**.[12,14] The results from the studies reviewed show there is 95% confidence that H-ADMs have a decrease

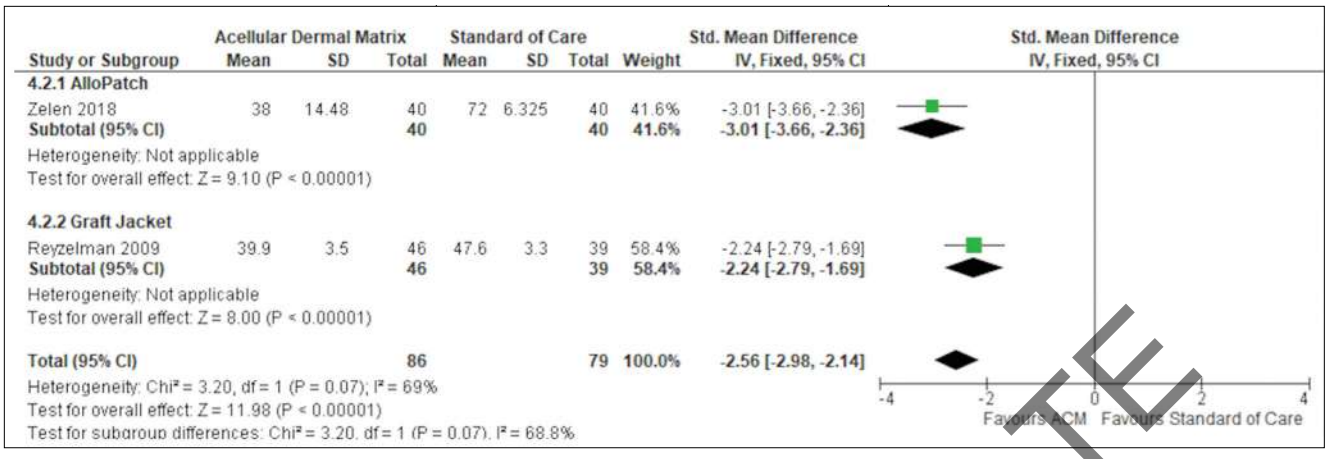

Figure 6. Forest plot of mean days to complete healing, grouped H-ADM vs. SOC
H-ADM: human-derived acellular dermal matrix; SOC: standard of care; CI: confidence interval

in mean time to complete healing (2.56 days times the standard mean difference fewer) over SOC (range, 2.98–2.14 days times the standard mean difference fewer) (Z = 11.98; *P* < .00001). In addition, there is 95% confidence that H-ADM Product C and H-ADM Product A subtypes have a decrease in mean time to complete healing of 2.24 days (range, 1.69–2.79 days; Z = 8.00; *P* < .0001) and 3.01 days (range, 2.36–3.66; Z = 9.10; *P* < .0001) in comparison with SOC, respectively. No studies had sufficient information to compare the mean time to complete healing for the H-ADM Product B subtype. When comparing between subtypes, tests for heterogeneity were not statistically significant (χ^2 = 3.20; df = 1; *P* = .07; I^2 = 69%; α = 0.05). This suggests the subtype were similarly statistically different to one another. A test for subtype differences showed a statistically significant difference between the subgroups (χ^2 = 3.20; df = 1; *P* = .07; I^2 = 68.8%), with H-ADM Product A significantly showing the most superiority of the 2 included groups when compared with SOC in days required for healing.

DISCUSSION

This study sought to provide a comprehensive meta-analysis of H-ADMs compared with SOC in the management of DFUs. A systematic review of the existing literature revealed 6 articles[9-14] that met inclusion criteria. Of the 6 articles, 2 were combined, as they shared data.[9,10] In evaluating the number of ulcers healed at 12 weeks, there was a significant and graphically obvious superiority of the treatment arm over SOC for overall effect (312 DFUs included). All individual studies,[11-14] except for the Walters et al[9] and Cazzell et al[10] combined data, showed superiority of H-ADM use. The discrepancy between the individual results of Walters et al[9] and Cazzell et al,[10] which favored H-ADM over SOC (**Figure 2**[9-14]), was likely due to the combined studies' weak effect sizes (log[OR] = 0.133) in comparison with the other studies'[11-14] effect sizes.

Of note, 3 studies[9-11] included data allowing for an analysis of complete DFU wound healing at 16 weeks. The overall effect of the data on 160 included ulcers significantly favored use of H-ADM over SOC. The combined data from Walters et al[9] and Cazzell et al[10] showed a point estimate favoring H-ADM, though the CI crossed the line of no effect. Although the original studies highlight a significant superiority of H-ADM (and specifically H-ADM Product B) over SOC at 16 weeks of follow-up, the present analysis for this time period disallows significant conclusions for this outcome. This is, again, likely due to an overall lower effect size when compared with Brigido.[11] In the Brigido study,[11] the results demonstrated clear superiority of H-ADM at 16 weeks. In terms of time to complete healing (in days), the forest plot (**Figure 4**[9-12,14]) demonstrates significant ($P = 1 \times 10^{-6}$) favor for the use of H-ADM, with all individual studies[12-14] echoing the overall effect results.

The sub-analysis aimed to compare H-ADM use versus SOC with data grouped by type of commercial H-ADM. The 3 H-ADM subtypes were represented in the forest plot (**Figure 5**[9-12,14]) investigating complete wound healing at 12 weeks; published RCTs with sufficient data for meta-analysis represented only these products at this time. The H-ADM Product C and H-ADM Product A showed significant superiority over SOC. While the H-ADM Product B's point estimate favored its use against SOC, the data were insignificant in the context of this comprehensive comparative analysis; again, this is likely due to lower effect size when compared with the other studies. Only H-ADM Product C and H-ADM Product A had sufficient data to be grouped in the sub-analysis for time to complete healing. Both of these products showed clear, significant superiority over SOC.

The present findings suggest the use of H-ADM may be more effective than typical SOC for DFU management; every outcome investigated in this study favored the use of H-ADM. When the data were grouped per specific commercial H-ADM product, each product's data at least trended toward superiority

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over SOC. Of note, H-ADM Product A showed slightly favorable data in terms of wounds healed at 12 weeks and overall days to healing, though comparator studies were plagued by significant heterogeneity. Prior studies have pooled existing data investigating the efficacy of DFU management with skin substitutes versus SOC. Santema et al[15] provided a 2016 systematic review and meta-analysis of DFUs managed with cellular and acellular skin substitutes as compared with SOC; 1655 randomized participants were included in that analaysis. Results suggested skin substitutes increased the likelihood of complete wound healing at 6 to 16 weeks (relative risk [RR], 1.55; 95% CI, 1.30–1.85).

Further, several of the included trials in the Santema et al analysis[15] compared 2 different types of skin substitutes. No specific type was found to be superior, though the types compared and study details were not specified.[15] Guo et al[16] conducted a systematic review and meta-analysis of the efficacy of ADMs for DFUs. While Guo et al[16] included many of the same studies as the present report, they did not distinguish between H-ADM and animal-derived ADMs and did not provide a sub-analysis of ADM brands. Outcomes investigated and results were similar to those reported herein; when compared with SOC, complete healing at 12 weeks and 16 weeks was higher for the H-ADM group (RR, 2.31; 95% CI, 1.42–3.76; and RR, 1.57; 95% CI, 1.28–1.93; respectively).

To the best of the authors' knowledge, this study is the first to provide a systematic review and meta-analysis specific to H-ADM use for DFU care. Further, the authors provide specific data and compare commercial brand H-ADMs in the subtype analysis.

LIMITATIONS

The present study has several limitations warranting mention. Inclusion criteria parameters specify H-ADM in an effort to increase internal validity. Still, the studies were significantly heterogeneous. Of note, the SOC utilized and frequency of H-ADM application was not consistent in the included studies. The patients of 2 included studies by Zelen et al[12,13] received weekly applications of new H-ADM dressings, while the rest[9–11,14] relied on a total of 1 or 2 sheets throughout the study time period. The H-ADM provides key peptides and growth factors inciting cell growth activation, in addition to offering extracellular matrix scaffolding key to the structural ingrowth of tissue and vasculature.

Although beyond the scope of this study, a significant difference in healing outcomes between wounds treated with a single application versus weekly H-ADM applications may imply a more powerful effect of growth factors versus cellular scaffolding — perhaps the structural contribution of the H-ADM is compromised by the frequent removal of the dressing. Further, SOC measures generally followed core principles of debridement, moist dressings, and pressure offloading; however, frequency of treatments, dressing materials, and methods of offloading differed. The overall heterogeneity between studies was addressed by utilizing a random effects model for analysis. Still, this calls into question the external validity of the data.

In addition, the studies failed to report results beyond 16 weeks of follow-up. Though a common endpoint, this follow-up length seems arbitrarily chosen. Research is needed with a longer follow-up period to more accurately assess the efficacy and best wound application regimen of H-ADMs.

Also, the total number of DFUs from the studies covered is relatively low. The available studies are few and often industry-associated, thus, the results are likely somewhat confounded by publication bias.

CONCLUSIONS

With the results and limitations in mind, H-ADM may increase the rate and short-term incidence of DFU healing when compared with SOC. Human-derived ADM shows significant superiority over SOC when evaluating DFUs completely healed at 12 and 16 weeks. Further, H-ADM demonstrates significant superiority over SOC when evaluating the number of days to complete DFU healing. Of commercially available H-ADMs included in this study, H-ADM Product A may demonstrate minimal superiority over H-ADM Product B and H-ADM Product C, though the data are limited and heterogeneous. Of note, H-ADM Product B did not significantly show superiority over the SOC. Further research is needed to better characterize the effects of H-ADM on DFUs at increased lengths of follow-up. More studies with larger sample sizes that are non-industry related are needed to investigate the efficacy and cost effectiveness of this treatment modality.

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