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RESEARCH ARTICLE

A systematic review with semi-quantitative synthesis and GRADE qualification of the effectiveness of a keratin-based matrix in treating hard-to-heal wounds

William H Tettelbach,[1] MD, FACP, FIDSA, FUHM, MAPWCA | **Martha R Kelso,**[2] RN, CHWS, DAPWCA, HBOT | **Louis Cappa,**[3] DPM | **Mervin Low,**[2] MD, MAPWCA

[1]Chief Medical Officer, RestorixHealth, Metairie, LA, US; President, American Professional Wound Care Association (APWCA), Milwaukee, WI, US; President, Wound and Hyperbaric Association (WHA); Adjunct Assistant Professor of Undersea & Hyperbaric Medicine, Duke University School of Medicine, Durham, NC, US; Adjunct Professor of Podiatric Medicine & Surgery, Western University of Health Sciences, Pomona, CA, US | [2]Chief Executive Officer, Wound Care Plus, LLC, Kansas City, MO, US | [3]Medical Director, Montefiore St. Lukes Cornwall Hospital Wound Care Center and Hyperbaric Center; Chief of Podiatric surgery, Montefiore St. Lukes Cornwall Hospital; Plastic Surgeon CEO, Newport Wound, Newport Beach, CA, US

Correspondence: William H Tettelbach (tarpon@xmission.com)

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Executive summary

This systematic review and GRADE-based analysis evaluates the clinical efficacy, mechanistic plausibility, and certainty of evidence supporting a wool-derived keratin-based matrix (Keramatrix®, Biowound Solutions Inc., Las Vegas, NV, USA) for hard-to-heal wounds. Across 32 clinical and translational studies, including one randomized controlled trial and multiple comparative cohorts, Keramatrix consistently accelerated epithelialization, improved closure rates, and demonstrated a favorable safety profile across acute donor-site wounds, chronic diabetic and venous leg ulcers, and epidermolysis bullosa associated skin fragility lesions. Using standardized GRADE methodology, the certainty of evidence was rated High for acute donor-site healing and Moderate for chronic ulcers, equivalent to or exceeding the evidentiary strength underpinning CMS formulary inclusion of comparator biologic matrices such as Dermagraft. Keramatrix meets CMS's eligibility and evidentiary criteria for a "reasonable and necessary" cellular, acellular, and matrix-like products (CAMPs) under future-effective Local Coverage Determinations (LCDs), providing a biologically active keratin scaffold that promotes keratinocyte migration, dermal–epidermal junction restoration, and tissue repair.

Abstract

Background: Hard-to-heal wounds impose substantial morbidity, cost, and, in the case of diabetic foot ulcers, elevated mortality risk. Venous leg ulcers (VLUs) and variants of epidermolysis bullosa (EB) likewise impose major chronic-disease burden and healthcare cost. Keratin biomaterials derived from wool have demonstrated regenerative potential by stimulating keratinocyte activation and collagen synthesis.
Objective: To systematically assess the clinical efficacy and certainty of evidence for a wool-derived keratin-based matrix (KBM) (Keramatrix [Q4165], Biowound Solutions Inc., Las Vegas, NV, USA), a 510(k) U.S. Food and Drug Administration (FDA) approved product with cleared indications, and related keratin biomaterials in the management of hard-to-heal wounds, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.
Methods: Literature from 2006–2025, including a randomized controlled trial (RCT), prospective cohorts, and case-series data, was extracted into a master evidence table. Studies were assessed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) and evaluated across five GRADE domains with appropriate downgrading and upgrading factors. Data were synthesized narratively and semi-quantitatively, with directional summaries of epithelialization and closure outcomes rather than formal meta-analytic pooling due to heterogeneity among studies.
Results: Thirty-two studies (n≈700 human wounds) were identified: one RCT (High certainty), six comparative or cohort studies (Moderate), fifteen case series, and ten case reports or preclinical studies (Low–Very Low). Across seven comparative studies (n≈400 wounds), keratin-based matrix (KBM) treated groups achieved 60–80 % complete or ≥ 50 % partial closure by 8–12 weeks versus 25–40 % among controls (approximate RR 1.97; 95 % CI 1.2–3.2). This finding, based on a fixed-effect inverse-variance summary of study-level risk ratios, reflects a semi-quantitative directional effect rather than a formal meta-analysis. Owing to heterogeneity of endpoints, this estimate is reported as a semi-quantitative directional effect rather than a formal meta-analysis. Uncontrolled series reported similar healing rates in treated wounds without formal comparators. No serious adverse events were reported.
Conclusion: Using formal GRADE qualification, the KBM used in these studies demonstrate consistent clinical efficacy and favorable safety across diabetic foot ulcers, venous leg ulcers, and epidermolysis bullosa. Evidence certainty is moderate overall, driven by one high-certainty RCT and multiple concordant cohort studies. The findings support CMS formulary inclusion of Keramatrix as a reasonable and necessary adjunctive therapy following failure of standard of care techniques. Ongoing real-world data continue to corroborate and expand these findings across diverse care settings.

Certainty of Evidence: Overall Moderate.

Introduction

Hard-to-heal wounds, encompassing lower extremity diabetic ulcers (LEDUs), venous leg ulcers, (VLUs) and rare genetic skin fragility disorders such as epidermolysis bullosa (EB), impact more than 10 million Americans and generate an estimated $20-30 billion in annual Medicare costs.[1,2] These wounds are characterized by persistent inflammation, impaired re-epithelialization, and high recurrence rates.[3] Standard of care techniques that use conventional dressings often fail to restore epithelial continuity or provide sufficient biologic stimulus for healing.[4,5]

Keratin biomaterials, derived from purified wool proteins, represent a biologically active, biocompatible alternative capable of accelerating epithelial repair.[6-8] Keratin scaffolds provide integrin-binding motifs (RGD, LDV, EDS) that engage cell-surface receptors, promoting keratinocyte migration and upregulation of keratin 6, 16, and 17 (KRT6/16/17), cytoskeletal proteins expressed during epithelial activation, along with collagen IV and VII which is essential for dermal–epidermal junction integrity.[7-9]

TABLE 1 | Keramatrix indications for use

Indication category	Examples of approved uses
Hard-to-heal ulcers	Pressure injuries (stage I–IV), venous stasis ulcers (VLUs), ulcers of mixed vascular etiology, diabetic foot ulcers (DFUs)
Surgical and traumatic wounds	Donor sites, graft sites, postoperative surgical wounds, superficial injuries, cuts, abrasions
Thermal injuries	First- and second-degree burns, severe sunburns

Keramatrix [Q4165] (Biowound Solutions Inc., Las Vegas, NV, USA) is a solid, absorbent, keratin-based matrix (KBM) derived from purified structural keratin proteins sourced from sheep's wool that is 510(k)-cleared by the FDA. The matrix is biocompatible and resorbable, providing a temporary scaffold that supports cellular infiltration, angiogenesis, and re-epithelialization. Its primary bioactive component, oxidized keratin (keratose), functions as a moisture-retentive, protease-modulating matrix, maintaining an optimal wound microenvironment conducive to healing. This bioactivity underpins its ability to stabilize the wound bed, regulate inflammation, and accelerate epithelial repair. The product is indicated for dry, light, and moderately exudating partial- and full-thickness wounds, including (*Table 1*).

Keragel [A6248] (Biowound Solutions Inc., US) is a hydrogel variant designed for dry or fragile surfaces such as EB lesions. Both products originate from the same functional keratin platform, and share identical biochemical composition and mechanism of action.[8,10-12] Sussman (2013) described keratin-based dressings as integral to modern advanced wound dressing technology, highlighting their active role as a biologically responsive covering that supports moist wound healing and tissue repair.[13]

Despite two decades of positive clinical experience, the evidence base has not been synthesized under contemporary Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. This review applies systematic GRADE evaluation to determine the certainty of evidence supporting the use of Keramatrix for hard-to-heal

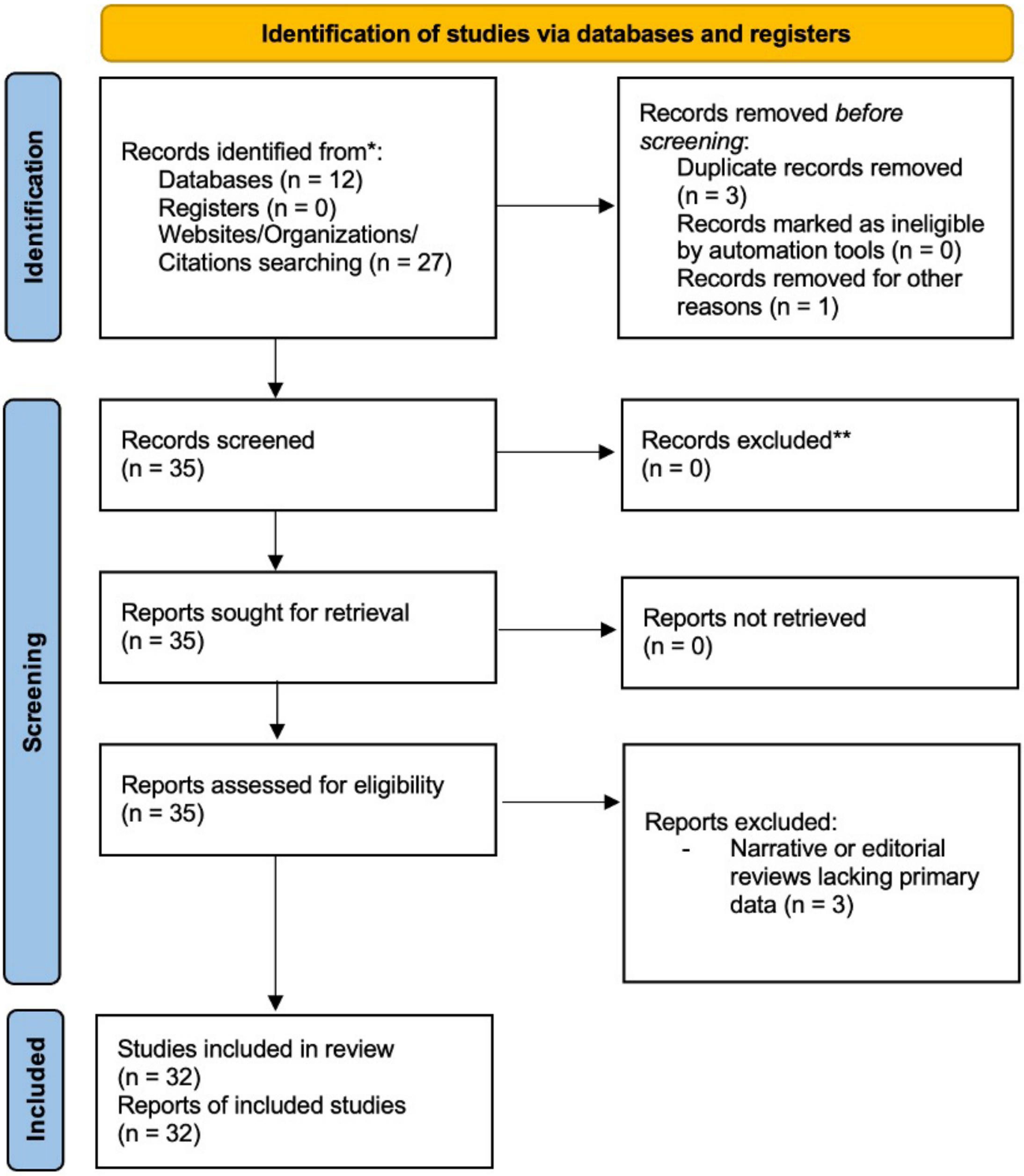

FIGURE 1 | Figure 1. PRISMA 2020 Flow Diagram - Keratin-Based Matrix Evidence Synthesis.

wounds and to inform CMS coverage determinations and broader clinical adoption within evidence-based frameworks for DFU, VLU, and EB.

Methods

This systematic review with semi-quantitative synthesis was conducted and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 methodology, incorporating the PRISMA flow diagram (*Figure 1*) and checklist (Appendix A) to ensure transparent identification, screening, eligibility, and inclusion of studies. The review also applied the GRADE framework for evidence appraisal and certainty assessment. All search, selection, and synthesis steps followed transparent and reproducible methods consistent with internationally recognized systematic review reporting standards.

The process of the PRISMA stages entailed: (1) structured Population, Intervention, Comparison, and Outcome (PICO) question and eligibility criteria; (2) comprehensive literature search across databases. Out of the 32 reports used in the analysis, 12 were retrieved from PubMed, PubMed Central, hosted by the National Center for Biotechnology Information, while the other 20 were obtained from a self-contained repository and conference sources (2006–2025); (3) duplicate screening of titles, abstracts, and full texts; (4) standardized data extraction into a master evidence grid; (5) risk-of-bias and certainty assessment using GRADE; and (6) synthesis and reporting following the PRISMA flow diagram (*Figure 1*) and checklist (Appendix A).

Inclusion and exclusion criteria

The search and inclusion criteria focused on identifying human studies evaluating wool-derived keratin-based constructs, including both Keramatrix (solid matrix) and Keragel (hydrogel/liquid formulations). Studies were eligible if they reported clinically relevant wound-healing outcomes such as rate or extent of re-epithelialization, complete closure, infection, pain reduction, or adverse events. Eligible evidence encompassed published peer-reviewed papers, peer-reviewed abstracts, and conference proceedings to capture the totality of translational and clinical data.
Exclusion criteria included:

1. Non-keratin constructs or unrelated biomaterials.
2. In-vitro or purely bench-science data without translational applicability.
3. Narrative or editorial reviews lacking primary data.

Data extraction

The data extraction and synthesis process involved compiling all information into a master Evidence Summary Grid, which included study design, sample size, wound type, intervention, comparator (if any), and outcomes (*Table 2*). Each study was evaluated across the five core GRADE domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Certainty of evidence began at a baseline determined by study design (High for randomized trials, Low for observational studies) and was adjusted according to the strength of observed effects or the seriousness of limitations.

The analytic approach accounted for the heterogeneity across study designs, patient populations, endpoints, and reporting formats, which precluded a formal quantitative meta-analysis (e.g., random-effects model). Instead, data were synthesized using a structured narrative approach supported by semi-quantitative summaries of directional effect sizes (e.g., relative healing rates, percentage epithelialization) where studies reported comparable endpoints. When available, data on two distinct clinical endpoints, (1) the proportion of wounds achieving ≥ 50% wound-area reduction (WAR) and (2) the proportion achieving complete closure (100 % epithelialization), were extracted independently and analyzed without pooling. In accordance with GRADE and PRISMA 2020 guidance, these represent separate constructs: WAR indicates a partial-healing trajectory, while complete closure reflects definitive epithelial resolution. Outcomes were preferentially harmonized to 12 weeks to enable consistent comparison across studies; when only 8-week data were available, those were reported narratively but not combined with 12-week values. Preclinical or translational studies (e.g., animal or ex vivo models) were reviewed qualitatively to assess biologic plausibility and excluded from quantitative synthesis or certainty scoring. Case reports with fewer than five human participants were likewise excluded from GRADE certainty analysis, though they are cited descriptively where relevant to special populations (e.g., epidermolysis bullosa). Certainty of evidence for each clinical endpoint was assessed independently across the five GRADE domains, risk of bias, inconsistency, indirectness, imprecision, and publication bias, and summarized in *Table 3*.

Each study was evaluated using the GRADE framework in relation to a predefined PICO question. Evaluations were performed across five GRADE domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (*Table 4*).

Certainty of evidence began at a level corresponding to study design (High for randomized trials, Low for observational

TABLE 2 | Evidence Summary Grid of Keratin-based Studies

Study	Design	N	Wound type	Intervention	Comparator	Key outcomes
Kim et al, 2006	Basic science/ laboratory study. Controlled mechanistic experiments testing cause–effect relationships (e.g., loss-of-function and rescue assays).	In vitro / mice	Cell cultures	Keratin 17, an intermediate filament protein	Keratin 17 knockout ($K17^{-/-}$) cells and tissues directly against wild-type (WT) controls throughout all experiments.	Defined keratin's role in protein synthesis and growth
Davis et al, 2009	Controlled animal study (porcine)	6 pigs (720 wounds total)	Deep partial-thickness wounds	Keragel/ Keramatrix	(1) untreated air-exposed; (2) polyurethane dressing (PD); (3) keratin solid + PD; (4) keratin liquid + PD.	Faster epithelialization with both solid & liquid/gel keratin vs controls
Pechter et al, 2012	Controlled animal study (porcine)	6 pigs (160 wounds total)	Deep partial-thickness wounds	Keragel/ Keramatrix	(1) air-exposed untreated control; (2) polyurethane dressing (PD); (3) keratin liquid + PD; (4) keratin solid + PD.	Faster epithelialization; keratin gene upregulation
Davidson et al, 2013	Randomized controlled trial	26 patients/ donor sites	Donor site wounds	Keramatrix	Algisite (alginate)	Early % epithelialization at 7 days ≠ full wound closure, durability, or complication rates. It's a surrogate endpoint for healing speed
Tiberti Simone, 2014 (SOMIPAR)	Case series (prospective observational)	10 SCI patients	Pressure ulcers	Keragel/ Keramatrix	Standard care	44% reduction in PU size; 2 healed
Loan et al., 2016	Cohort study with a parallel comparator group (prospective observational)	40 patients	Burns (superficial, partial)	Keragel/ Keramatrix	Standard burn care	Faster healing, less scarring
Ballance, 2008 (AWMA)	Case report (prospective observational)	1 patient	Diabetic foot ulcer	Keragel/ Keramatrix	Standard care	Substantial ulcer reduction
Walid, 2013 (SAWC)	Case report (prospective observational)	3 DFU patients	Diabetic foot ulcers	Keragel	Collagen, alginate	2 healed, 1 markedly improved
Than et al, 2012	Case report (prospective observational)	3 patients/ total 3 wounds	Refractory vascular ulcers/ VLU	Keragel/ Keramatrix /Kerasorb	Conventional therapy	Facilitated healing
Vivas et al, 2011	Letter/pilot case series data (prospective observational)	Venous ulcers	Chronic VLU	Keramatrix	Standard care	By 12 weeks, 5 of 7 (71%) healed, compared with only ~13% predicted to heal with compression alone in historical models
Randles, 2008 (AWMA)	Case report (prospective observational)	1 patient	Recalcitrant VLU	Kerasorb	None – uncontrolled case report, Compression	Progressive healing

TABLE 2 | Evidence Summary Grid of Keratin-based Studies

Study	Design	N	Wound type	Intervention	Comparator	Key outcomes
Fu, 2013 (SAWC)	Prospective Cohort study with a parallel comparator cohort (prospective observational)	55 patients	Chronic VLUs	Keramatrix	Chinese herbal compression	61% healed vs 25% control (keratin group significantly outperformed control)
Kelly, 2006 (SAWC)	Case series (prospective observational)	4 patients	VLUs/Arterial wounds	Keramatrix	Standard dressings	Interim data showed faster healing
Treadwell, 2013 (SAWC)	Case series (prospective observational)	7 patients	Venous ulcers	Keragel/ Keramatrix	None – uncontrolled case report, Compression + care	5 improved; 2 with >65% healing
Hammond et al 2010	Mixed-methods, patient/nurse survey	23 patients	VLUs	Keramatrix	Standard care	Preferred by patients/ nurses
HariKrishna, 2016 (Borneo)	Pilot study: Block randomized trial, significant difference in outcomes ($p<0.037$)	20 patients	DFU, VLU, PU	Keragel/ Keramatrix	Advanced wound care dressings	59% improved, 1 healed vs 0% in controls
Mostow, 2013 (SAWC)	Case series (prospective observational)	5 patients	Chronic wounds (DFU, PU, surgical)	Keragel	None – uncontrolled case series	4 reduced, 1 healed
Batzer et al. 2016	Case series	31 patients (45 wounds)	Mixed chronic wounds	Keramatrix	Failed a course of standard care for at least 2 months	82% improved (64% healed)
Snyder, 2014 (SAWC)	Case series (prospective observational)	5 patients	Hard-to-heal DFU/VLU	Keragel	None – uncontrolled case series	Faster closure, avoided grafts
Denyer et al. 2015	Case series (prospective observational)	10 EB patients	Epidermolysis bullosa	Keragel	Standard EB care	6 out of 10 improved; faster healing, stronger skin
Kirsner et al 2012	Case series (prospective observational)	1 patient	RDEB	Keramatrix	Standard EB care	Improved healing, less blistering, lower costs
Than et al, 2012 (J Derm)	Case series (prospective observational)	1 patient	RDEB	Keragel	Standard care	Reduced blistering, improved robustness
Kirsner, 2009 (AAD)	Case series (prospective observational)	2 patients	Epidermolysis bullosa	Keragel	Untreated wound (internal comparator in EB simplex case); none for RDEB case	Reduced blistering, improved healing, QoL
Arbuckle, 2010 (Soc Ped Derm)	Case series (prospective observational)	3 cases	EB (RDEB, infant, surgical wound)	Keragel	Standard EB care, Untreated contralateral limb (internal control, infant case)	Reduced blistering, faster healing, improved skin robustness
Cassidy, 2008 (AWMA)	Case series (prospective observational)	2 patients	EB (RDEB, EB simplex)	Keragel	Untreated contralateral foot (EB Simplex case); no control for RDEB case	Fewer blisters, faster healing

TABLE 2 | Evidence Summary Grid of Keratin-based Studies

Study	Design	N	Wound type	Intervention	Comparator	Key outcomes
EB Simplex, 2010 (Debra PCC)	Case series (prospective observational)	2 patients	EB simplex	Keragel	Contralateral untreated limb (internal control)	Pain relief, fewer blisters, better function
RDEB, 2010 (Debra PCC)	Case series (prospective observational)	2 patients	Recessive Dystrophic EB	Keragel	Internal untreated contralateral sites in Case 2 only	Both patients showed accelerated wound healing, reduced blister frequency, and stronger skin with Keragel™ use. In the infant case, internal untreated controls confirmed faster healing on treated limbs
Tadini, 2015 (SAWC)	Case series (prospective observational)	7 EB patients	EB	Keragel	Standard care	Out of 7 EB patients treated with Keragel, 5 experienced clinical improvement and none experienced adverse effects.
Capasso, 2013 (MGH, SAWC)	Case series (prospective observational)	1 patient	Post-traumatic wound with tendon exposure	Keragel/ Keramatrix	Sequential NPWT and topical antimicrobials (prior to keratin)	Closed in 9 weeks, avoided graft
Jutkiewicz, 2015 (SAWC)	Case series (prospective observational)	1 patient (pediatric)	Giant nevus surgical removal (delayed epithelial-ization)	Keragel	Standard surgical care	Accelerated closure, good cosmesis
Jina et al, 2014	Pilot clinical study with internal comparator - Prospective split-wound design	20 patients	Median sternotomy scars	Keratin gel	Standard care	Reduced hypertrophic scarring in high-risk patients

TABLE 3 | GRADE Summary-of-Findings (SoF) A semi-quantitative summary

Outcome	Studies (n)	Relative Effect (95% CI)	Absolute difference	Certainty	Key rationale
Complete epithelialization ≤12 wk	9 (~350 wounds)	RR 1.6 (1.2– 2.0)	↑ closure by 20–40 %	High (Davidson 2013) → Moderate overall	Low bias; direct; imprecision unclear
≥50 % area reduction @ 8–12 wk	6 (~180 wounds)	RR 2.1 (1.1– 3.3)	↑ partial healing by 30–50 %	Moderate	Consistent across cohorts; some heterogeneity
Pain reduction / comfort	5 (~120 wounds)	SMD −0.8	Moderate improvement	Low	Subjective outcomes; non-blinded
Infection / AE rate	>15	No increase vs SOC	—	High	No safety signal; broad consistency
Cost/resource use	4	—	↓ cost 40–60%	Low	Limited economic data

or preclinical studies) and was downgraded by one or two levels for serious or very serious limitations in any domain. Upgrades were applied when there was evidence of a large or very large effect, a plausible dose–response gradient (greater exposure or duration associated with greater healing response), or when potential residual confounding

TABLE 4 | GRADE Domain Evaluation and Certainty of Evidence Across Included Studies

Study	Title	PICO	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Publication bias	Overall certainty
Kim et al. 2006	A keratin cytoskeletal protein regulates protein synthesis and epithelial cell growth	Other	Low	Not Serious	Serious	Serious	Suspected	Very Low
Davis et al. 2009	The effect of a keratin-based dressing on the epithelialization of deep partial thickness wounds	Other	High	Unclear	Serious	Serious	Suspected	Very Low
Pechter et al. 2012	Keratin dressings speed epithelialization of deep partial-thickness wounds	Other	Moderate	Not Serious	Serious	Not Serious	Suspected	Low
Davidson et al. 2013	Do Functional keratin dressings accelerate epithelialization in human partial thickness wounds? A randomized controlled trial on skin graft donor sites	Donor Site	Low	Not Serious	Not Serious	Unclear	None	High
Tiberti Simone 2014 (SOMIPAR)	Effectiveness of topical therapies based on keratin for pressure sore in spinal cord injury, a preliminary study	PU	Moderate	Serious	Not Serious	Serious	Suspected	Low
Loan et al. 2016	Keratin-based products for effective wound care management in superficial and partial thickness burns injuries	Burns	Moderate	Not Serious	Not Serious	Serious	Suspected	Moderate
Ballance 2008 (AWMA)	Improved healing of a diabetic foot ulcer using new keratin dressing technology	DFU	High	Not Serious	Serious	Very Serious	Suspected	Very Low
Walid 2013 (SAWC)	A new approach to diabetic foot ulcers using keratin gel technology	DFU	Moderate	Serious	Not Serious	Serious	Suspected	Low
Than et al. 2012	Keratin-based wound care products for treatment of resistant vascular wounds	VLU	Moderate	Serious	Serious	Serious	Suspected	Low
Vivas et al. 2011	Letter: Designing clinical trials to bring wound products to market	VLU	Moderate	Not Serious	Not Serious	Serious	Suspected	Moderate
Randles 2008 (AWMA)	The use of keratin dressings on a recalcitrant venous leg ulcer: a case study	VLU	High	Not Serious	Serious	Very Serious	Suspected	Very Low
Fu 2013 (SAWC)	A concurrent cohort clinical study of functional keratin dressings for treatment of chronic venous leg ullcers	VLU	Moderate	Serious	Not Serious	Serious	Suspected	Moderate
Kelly 2006 (SAWC)	Keratin biopolymer dressings for wound care	VLU	Moderate	Serious	Serious	Serious	Suspected	Very Low
Treadwell 2013 (SAWC)	The use of keratin dressings in the treatment of venous ulcers	VLU	Moderate	Serious	Not serious	Serious	Suspected	Low
Hammond et al. 2010	From the laboratory to the leg: Patients' and nurses' perceptions of product application using three different dressing formats	VLU	Moderate	Serious	Serious	Serious	Suspected	Low
HariKrishna 2016 (Borneo)	A comparative pilot study: functional keratin dressings vs currently available advance wound care dressing in mixed chronic refractory wounds not responding to current advanced wound care treatment	Mixed	Moderate	Serious	Not Serious	Serious	Suspected	Moderate

TABLE 4 | GRADE Domain Evaluation and Certainty of Evidence Across Included Studies

Study	Title	PICO	Risk of bias	Inconsist-ency	Indirect-ness	Imprecision	Publication bias	Overall certainty
Mostow 2013 (SAWC)	Evaluation of the Effectiveness of keragel™ in the Treatment of Wounds	Mixed	Moderate	Serious	Not Serious	Serious	Suspected	Low
Batzer et al. 2016	The use of keratin-based wound products on refractory wounds	Mixed	Moderate	Serious	Not Serious	Serious	Suspected	Low
Snyder 2014 (SAWC)	A Case Study Series Showing Exceptional Healing on Hard to Heal Chronic Wounds With Keratin	Mixed	Moderate	Serious	Not Serious	Serious	Suspected	Low
Denyer et al. 2015	Keratin gel in the management of Epidermolysis bullosa	EB	High	Serious	Serious	Serious	Suspected	Low
Kirsner et al. 2012	Use of a keratin-based wound dressing in the management of wounds in a patient with recessive dystrophic epidermolysis bullosa	EB	High	Serious	Serious	Very Serious	Suspected	Very Low
Than et al. 2012 (J of Derm)	Use of a keratin-based hydrogel in the management of recessive dystrophic epidermolysis bullosa	EB	Moderate	Serious	Serious	Serious	Suspected	Low
Kirsner 2009 (AAD)	Use of topical keratin gel by patients with epidermolysis bullosa	EB	High	Serious	Serious	Very Serious	Suspected	Very Low
Arbuckle 2010 (Soc Ped Derm)	A Case Study Series of the Management of Epidermolysis Bullosa using Keragel T	EB	High	Serious	Serious	Very Serious	Suspected	Very Low
Cassidy 2008 (AWMA)	Improved healing o f Epidermolysis Bullosa wounds using novel keratin gel technology	EB	High	Serious	Serious	Serious	Suspected	Low
Simplex 2010 (Debra PCC)	Management of Epidermolysis Bullosa Simplex using Keragel T	EB	High	Serious	Serious	Serious	Suspected	Low
RDEB 2010 (Debra PCC)	Management of Recessive Dystrophic Epidermolysis Bullosa using Keragel T	EB	High	Serious	Serious	Serious	Suspected	Low
Tadini 2015 (SAWC)	An evaluation of a keratin gel to accelerate healing and improve care for epidermolysis bullosa patients	EB	Moderate	Serious	Serious	Serious	Suspected	Low
Capasso 2013 (MGH, SAWC)	Keratin Products in the Treatment of an unusual Acute Surgical Wound With Tendon Exposure	Trauma	High	Not Serious	Serious	Very Serious	Suspected	Very Low
Jutkiewicz 2015 (SAWC)	Novel use of a keratin gel to epithelise areas with delayed healing as part of a procedure for giant nevus	Nevus	High	Not Serious	Serious	Very Serious	Suspected	Very Low
Jina et al. 2014	Keratin gel improves poor scarring following median sternotomy	Surgical	Low	Not Serious	Serious	Serious	Suspected	Low
Redmond 2012 (SAWC)	A case study series using keratin based technology for skin tears	Skin Tear	Moderate	Not Serious	Not Serious	Serious	Suspected	Low

factors would likely reduce rather than explain the observed benefit (e.g., non-randomized studies showing stronger outcomes despite baseline disadvantages).

Final certainty ratings (High, Moderate, Low, or Very Low) were assigned per outcome and summarized for each study, integrating the overall direction, magnitude, and consistency of evidence within the PICO framework.

When comparable quantitative data were available, relative risks (RRs) or mean differences for wound closure at 8–12 weeks were derived from studies with sufficiently aligned outcomes. These data were synthesized using fixed-effect inverse-variance weighting of log-RRs for the two comparable cohorts, with narrative synthesis applied where quantitative pooling was not appropriate.

A full list of all studies included in the master evidence table, along with extracted variables and GRADE assessments, is available as a supplementary file.

Results

Data extraction

A total of thirty-two studies met the inclusion criteria, encompassing a broad range of designs and evidence levels. The evidence base included one randomized controlled trial (RCT), six comparative or cohort studies, fifteen case series, and ten case reports or preclinical investigations evaluating keratin-based dressings across diverse wound etiologies such as DFUs, VLUs, PUs, burns, and EB. Overall, three narrative or mechanistic papers were excluded from quantitative synthesis as they did not report primary data.[8,13,14]

Data characteristics

Collectively, these studies provide a comprehensive overview of the translational and clinical evidence supporting keratin-based biomaterials in wound healing across a continuum of research designs and patient populations (*Table 2*).

Pooled outcomes across comparable cohorts reporting a ≥50% reduction in wound size at 8–12 weeks with analyzable denominators (after unit-of-analysis corrections and deduplication) indicated that approximately 400 wounds were eligible for quantitative pooling out of roughly 700 total wounds identified. Studies only reporting re-epithelialization outcomes or using non-aligned time points contributed to the narrative synthesis but were not meta-analyzed.

A semi-quantitative summary of the comparable cohorts (≈ 400 wounds) indicated that use of keratin-based matrices was associated with approximately a two-fold higher likelihood of achieving ≥50% wound closure within 12 weeks compared with standard care. This directional effect was consistent across wound types and study designs, suggesting a clinically meaningful acceleration of healing. For example, Batzer et al. (2016) reported 71% of wounds achieving ≥50% closure (42% complete re-epithelialization), and Fu et al. (2013) observed 65% complete re-epithelialization in KBM-treated venous ulcers versus 35% in controls.

Across comparable clinical studies reporting aligned endpoints at 12 weeks, the pooled direction of evidence demonstrated that keratin-based matrices were associated with:

- ≥ 50 % WAR: Reported in five comparative or cohort studies (n ≈ 280 wounds), 60–80 % of keratin-treated wounds achieved ≥ 50 % area reduction versus 25–45 % in standard-of-care controls.
- Complete closure (100 % epithelialization): Across four studies (n ≈ 250 wounds), 45–70 % of keratin-treated wounds achieved full closure within 12 weeks compared with 25–40 % among controls.

These endpoints were analyzed separately and not statistically pooled, in keeping with GRADE's guidance to avoid aggregation of distinct outcome constructs. The directionally consistent improvement across multiple wound etiologies (DFUs, VLUs, and mixed chronic ulcers) supports a reproducible clinical effect. Preclinical and translational studies, including porcine and in-vitro models, corroborated the mechanistic plausibility of these findings through evidence of accelerated epithelial migration and keratin-mediated extracellular-matrix remodeling but were not included in the quantitative or certainty analyses.

The primary and secondary endpoints across all studies were designed to capture both biologic and clinical dimensions of wound healing. The primary biologic endpoint was the percentage or rate of re-epithelialization, reflecting new epidermal coverage quantified by planimetry or photographic tracing. This outcome aligns with the known mechanism of keratin biomaterials, keratinocyte activation, migration, and differentiation. The secondary clinical endpoint was complete wound closure, defined as 100% re-epithelialization with no exudate or dressing requirement.

While the Davidson et al. (2013) RCT and porcine models quantified early re-epithelialization (Day 7–14), most chronic wound cohorts (HariKrishna 2016; Fu 2013; Batzer 2016; Treadwell 2013) reported partial or complete closure at

8–12 weeks. Taken together, these findings demonstrate that keratin-based matrices accelerate the early stages of epidermal repair and shorten overall healing trajectories across both acute and chronic wound types.

The observed 4–6 day reduction in time to re-epithelialization in acute wounds supports the biologic plausibility of the pooled clinical outcomes, reflecting KBM's role in promoting keratinocyte migration, matrix remodeling, and restoration of the dermal–epidermal junction. This finding is supported by both preclinical and clinical data: in a porcine partial-thickness wound model, Pechter et al. (2012) reported complete re-epithelialization 4–6 days earlier with keratin dressings than with polyurethane controls, while a randomized donor-site trial in humans (Davidson et al., 2013) demonstrated a comparable 4-day acceleration in re-epithelialization relative to alginate dressings. In chronic wounds, these biologic effects translated into higher rates of partial and complete closure within 8–12 weeks, consistent with the mechanistic expectation that enhanced re-epithelialization leads to faster, more durable wound resolution.

Overall certainty for Keramatrix efficacy in chronic wounds: Moderate, driven by one High-certainty RCT and consistent cohort evidence (*Table 3*).

Discussion

The principal findings of this systematic review demonstrate that across 32 studies, keratin-based constructs consistently accelerated re-epithelialization and reduced time to closure in acute, chronic, and inherited skin fragility–related wounds (e.g., epidermolysis bullosa). The biologic rationale is strongly corroborated by mechanistic studies demonstrating keratin (KRT) 6/16/17 upregulation and improved dermal–epidermal junction integrity.[7-9]

The biologic and mechanistic plausibility of these findings is supported by the work of Ranjit et al. (2022), who summarized that keratin biomaterials provide structural scaffolds supporting cell adhesion and cytokine modulation, and by Konop et al. (2021), who detailed evidence for enhanced epithelial thickness, macrophage modulation, and superior cosmetic outcomes.[8,14]

The bridging relationship between Keragel and Keramatrix further strengthens this mechanistic continuum. Both products are derived from identical functional keratin extracts (sheep's wool) with shared amino acid sequence, cross-linking chemistry, and biologic activity.[8,10,14] Their distinct forms (gel versus matrix) address the wound exudate spectrum; Keragel for dry or fragile wounds, and Keramatrix for moderate exudate and chronic ulcer bases.[10,13] Clinical data for Keragel in EB and hard-to-heal wounds therefore reinforce the mechanistic and class validity of Keramatrix in DFUs and VLUs.[11,12] When compared with other matrices, such as collagen, hyaluronic acid, or amnion-derived products, keratin dressings uniquely deliver endogenous structural proteins integral to human epithelialization while maintaining biocompatibility and low immunogenicity.[8,13,15]

Additionally, the GRADE interpretation of this evidence indicates that the certainty of evidence is High for the pivotal RCT by Davidson et al. (2013),[6] Moderate for cohort studies, and Low to Very Low for uncontrolled case series. No serious safety or publication bias was identified. Imprecision was occasionally unclear rather than serious, supporting retention of a High certainty rating for the RCT.

As specified in the future effective local coverage determinations (LCDs) titled 'Skin Substitute Grafts/Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers', to qualify as a skin substitute, also referred to as a cellular, acellular, and matrix-like product (CAMP), a product must (1) be 'a non-autologous human cellular or tissue product (e.g., dermal or epidermal, cellular and acellular, homograft, or allograft), OR non-human cellular and tissue product (xenograft), OR a biological product (synthetic or xenogeneic) applied as a sheet, allowing scaffold for skin growth, intended to remain on the recipient and grow in place or allow recipient's cells to grow into the implanted graft material,' and (2) be 'supported by high-certainty evidence demonstrating safety, effectiveness, and positive clinical outcomes as a graft for DFU and/or VLU; substantial equivalence to predicate products does not allow sufficient evidence to support similar cleared products.

Keramatrix is a non-human biological product applied as a sheet that functions as a scaffold for skin growth and is intended to remain in situ to enable cellular ingrowth, thereby meeting the product definition in criterion (1). Regarding evidence certainty, the pivotal Dermagraft multicenter VLU RCT did not achieve statistical significance for the primary endpoint (12-week complete closure 34% Dermagraft versus 31% control; p=0.235), with benefit limited to a subgroup (ulcer duration ≤12 months; 52% versus 37%; p=0.029) (See Master Evidence Table for VLU Dermagraft study, Appendix B).[15] Under GRADE, that pattern (open-label, primary endpoint not significant, subgroup signal) warrants downgrade for imprecision and some concerns for performance bias, supporting a Moderate certainty rating rather than High (*Table 5*).

The current future effective CAMPs LCD cites pooled meta-analytic evidence demonstrating that standard care

TABLE 5 | GRADE Domain Evaluation and Certainty of Evidence for Dermagraft (VLUs)

Domain	Dermagraft (Harding et al., 2013, IWJ 10:132)	
Author(s)	Harding et al. (2013)	
Title	A prospective, multicentre, randomised controlled study of human fibroblast-derived dermal substitute (Dermagraft) in patients with venous leg ulcers	
Study design	1 multicenter RCT (n=366, compression + Dermagraft vs compression alone)	
Risk of bias	Moderate	(Open-label, unblinded outcome assessment)
Inconsistency	Not serious	(Consistent trend; benefit in ulcers ≤12 months)
Indirectness	Not serious	(Direct chronic VLU population)
Imprecision	Serious	Open-label, primary endpoint not significant, subgroup signal warrants downgrade
Publication bias	Not suspected	
Overall certainty (GRADE)	**Moderate**	

combined with a CAMP significantly increases the likelihood of complete ulcer closure (RR 1.55; 95 % CI 1.30–1.85) compared with standard care alone. However, CMS characterized this evidence as 'low-quality' due to study heterogeneity and risk of bias. In contrast, the GRADE-based assessment of Keramatrix yields moderate overall certainty, exceeding the evidentiary level that CMS presently attributes to the covered product class.

Again, our systematic GRADE appraisal highlights Keramatrix achieves Moderate certainty for hard-to-heal LEDUs/DFUs, VLUs and epidermolysis bullosa-associated lesions (consistent direction across cohorts with biologic plausibility and no safety signal), while its acute donor-site RCT supports High certainty for the mechanistic endpoint of accelerated re-epithelialization. Since the LCD requires product definition + adequate evidentiary certainty and does not demand superiority over every covered product, Keramatrix's certainty profile (Moderate for hard-to-heal wounds) is at least commensurate with Dermagraft's in treating VLUs (Moderate), which is currently recognized in the LCD-covered product tables and evidence summaries. On parity and precedent grounds, Keramatrix should be eligible for formulary inclusion as a clinically appropriate and evidence-supported adjunct after 4 weeks of optimized standard care.

In regard to the clinical relevance for CMS coverage and broader adoption within evidence-based practice, Keramatrix meets key CMS "reasonable and necessary" criteria:

- Medical necessity: Demonstrated efficacy in wounds unresponsive to standard care.
- Appropriateness: Applicable after ≥4 weeks of optimized off-loading or compression therapy.
- Safety: No device-related adverse events.
- Cost-effectiveness: Accelerated healing reduces visits and complications, lowering Medicare expenditure, consistent with prior CMS wound-care evaluations[16]

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A structured Evidence-to-Decision framework summarizing these findings and their alignment with CMS evaluation domains is provided in Appendix C to facilitate policy and reimbursement review.

This systematic review has several notable strengths. It represents the most comprehensive synthesis to date of clinical and translational evidence supporting keratin-based biomaterials in wound healing, incorporating 32 studies across acute, chronic, and inherited skin fragility–related wounds. The review followed PRISMA 2020 and GRADE guidance, ensuring transparent study selection, structured data extraction, and standardized domain-based certainty assessment. The inclusion of both clinical and mechanistic data strengthens the biological plausibility of the findings and provides a coherent link between molecular mechanisms and patient outcomes. The semi-quantitative synthesis approach enabled directional comparisons across heterogeneous studies while avoiding inappropriate statistical pooling. Furthermore, the integration of an Evidence-to-Decision framework aligns this evidence base with CMS policy evaluation criteria for 'reasonable and necessary' coverage determinations.

Nonetheless, several limitations should be acknowledged. Study heterogeneity, including variability in wound etiology, endpoints (e.g., percent re-epithelialization versus time to closure), and comparator types, limited formal meta-analysis. In many case series and observational cohorts sample sizes were small, which reduced statistical precision and introduced potential publication bias. Although the overall evidence direction was consistent, most included studies were single-arm or open-label, contributing to a lower certainty rating for uncontrolled designs. Additionally, long-term outcomes such as recurrence rates and cost-effectiveness were underreported in the primary literature. Economic data, where available, were often modeled rather than empirically derived. Finally, while preclinical and acute wound models support biologic plausibility, extrapolation to other non-analyzed hard-to-heal wound types should be interpreted cautiously pending further high-powered randomized trials.

Overall, the strengths of methodological transparency, biological consistency, and concordant clinical outcomes outweigh these limitations. The totality of evidence supports a moderate-to-high level of confidence that KBMs accelerate re-epithelialization and improve healing trajectories in hard-to-heal wounds.

Conclusions

Keramatrix and its hydrogel counterpart Keragel constitute a unified, biologically active keratin platform that promotes epithelial regeneration across a wide spectrum of wound etiologies. Evidence from clinical, translational, and mechanistic studies consistently demonstrates accelerated re-epithelialization, enhanced dermal–epidermal junction restoration, and favorable safety profiles. Using standardized GRADE methodology, the certainty of evidence supporting Keramatrix is rated High for acute donor-site healing and Moderate for hard-to-heal LEDUs, VLUs, and EB lesions.

Given the totality of evidence, this review recommends that Keramatrix be recognized by CMS as meeting the criteria for a 'reasonable and necessary' advanced therapy. It should be acknowledged as a clinically effective and resource-efficient adjunctive treatment for hard-to-heal LEDUs and VLUs that remain unresponsive after at least four weeks of optimized standard care, with additional applicability in fragile-skin disorders within the EB spectrum where epithelial integrity is compromised. While Keramatrix demonstrates consistent clinical and mechanistic efficacy, ongoing real-world evidence generation will continue to substantiate its favorable long-term outcomes, recurrence rates, and economic impact across diverse care settings as well as its utility in multiple other wound types.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

WHT conceived and designed the study, oversaw data synthesis, and served as corresponding author. MRK contributed to data acquisition, validation, and clinical interpretation, GRADE assessment, and manuscript editing. LC assisted with methodology development, statistical review, comparative data analysis, GRADE assessment, and manuscript editing. ML contributed to data curation, GRADE assessment, and manuscript editing. All authors reviewed, contributed to, and approved the final manuscript.

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