Efficacy of MMP-inhibiting wound dressings in the treatment of hard-to-heal wounds: a systematic review

Objective: Matrix metalloproteinases (MMPs) substantially contribute to the development of chronicity in wounds. Thus, MMP-inhibiting dressings may support healing. A systematic review was performed to determine the existing evidence base for the treatment of hard-to-heal wounds with these dressings.
Methods: A systematic literature search in databases and clinical trial registers was conducted to identify randomised controlled trials (RCTs) investigating the efficacy of MMP-inhibiting dressings. Studies were analysed regarding their quality and clinical evidence.
Results: Of 721 hits, 16 relevant studies were assessed. There were 13 studies performed with collagen and three with technology lipido-colloid nano oligosaccharide factor (TLC-NOSF) dressings. Indications included diabetic foot ulcers, venous leg ulcers, pressure ulcers or wounds of mixed origin. Patient-relevant endpoints comprised wound size reduction, complete wound closure, healing time and rate. Considerable differences in the quality and subsequent clinical evidence exist between the studies identified. Substantial evidence for significant improvement in healing was identified only for some dressings.
Conclusion: Evidence for the superiority of some MMP-inhibiting wound dressings exists regarding wound closure, wound size reduction, healing time and healing rate. More research is required to substantiate the existing evidence for different types of hard-to-heal wounds and to generate evidence for some of the different types of MMP-inhibiting wound dressings.
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clinical evidence • hard-to-heal wounds • matrix metalloproteinases (MMPs) • MMP-inhibiting wound dressings • wound healing

Hard-to-heal wounds are often defined as wounds with delayed or stagnated healing that fail to heal within eight weeks.[1] If these wounds are not treated appropriately, they can last for several months or even years and may become severe.[2] Frequently occurring hard-to-heal wounds, including diabetic foot ulcers (DFU), venous leg ulcers (VLU) and pressure ulcers (PU), represent a significant burden on economic health and social care costs as well as the patient's quality of life (QoL).[3–5] Therefore, accelerating the healing process is of particular importance in order to improve patient QoL and to reduce healthcare costs.

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The role of matrix metalloproteinases in wound healing

Research, on the course of physiological wound healing and those wounds developing chronicity, uncovered key roles for matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs).[2,6–10] MMPs are a family of more than 20 structurally related endopeptidases involved in many physiological processes, such as cell signaling, cell migration, angiogenesis and the degradation of extracellular matrix (ECM) proteins.[11] Wound healing mainly involves MMP-1, -2, -3, -7, -13 and -26.[2,11,12] In physiological wound healing they ensure the breakdown of damaged tissue at the start of the healing process.[12] However, in the later stages of wound healing, increased MMP activity is undesirable since it is thought that MMPs inhibit the formation of new tissue. At these stages of wound healing, TIMP play an essential role, as they downregulate MMP activity.[9,10] In hard-to-heal wounds, this control appears to be impaired, resulting in an imbalance between MMP and TIMP ratio.[13] Consequently, healing is delayed or even stagnated and inflammation is prolonged.[12,14] Evidence suggests that elevated MMP-levels correlate with delayed healing in

Table 1. Overview of keywords used for literature search

Generic term	Synonyms	Subtopic	MeSH Terms [mh], Substance [nm]
Chronic wounds	chronic wound chronic wounds chronic AND wound chronic AND wounds chronic injury chronic injuries chronic AND injury chronic AND injuries chronic sores chronic AND sores	leg AND (ulcer OR ulcers OR ulceration) varicose AND (ulcer OR ulcers OR ulceration) foot AND (ulcer OR ulcers OR ulceration) decubitus AND (ulcer OR ulcers OR ulceration) pressure AND (ulcer OR ulcers OR ulceration) skin AND (ulcer OR ulcers OR ulceration) ulcus cruris bed sore bedsore bed sores bedsores	wounds and injuries[mh] AND chronic leg ulcer[mh] varicose ulcer[mh] pressure ulcer[mh] diabetic foot[mh]
MMP-inhibition	matrix metalloproteinase AND inhibit* matrix metalloproteinases AND inhibit* matrix metalloprotease AND inhibit* matrix metalloproteases AND inhibit* matrix metallo-proteinase AND inhibit* matrix AND metalloproteinases AND inhibit* mmp AND inhibit* mmps AND inhibit* mmp* AND inhibit*	nano-oligosaccharide factor sucrose octasulfate TLC-NOSF polyhydrated ionogen collagen (oxidized OR oxidated) AND regenerated cellulose Promogran DerMax Tegaderm Matrix MelMax Suprasorb	matrix metalloproteinases[mh] AND inhibit* matrix metalloproteinases[nm] AND inhibit*
Wound dressing	bandage bandages dressing dressings		bandages[mh]
Wound healing, wound size reduction	area reduction surface reduction wound healing wound healing wound AND reduction	wound closure	wound healing[mh]

patients with many different types of hard-to-heal wounds including DFU, VLU and PU.[15–18]

Development of MMP-inhibiting wound dressings

Taking into account the deleterious role of MMPs in hard-to-heal wounds, dressings that regulate these molecules could support the healing process. Wound dressings that are able to reduce MMP activity have been developed for the treatment of hard-to-heal wounds on the basis of *in vitro* and animal model data.[19–23] Oxidised regenerated cellulose (ORC)/collagen matrix, which came onto the market at the end of the 1990s, was the first product of this kind. Collagen has protease-inactivating properties, promotes haemostasis and reduces inflammatory mediators, leading to changes in wound microenvironment.[19,24–27] Results of clinical trials with patients with a VLU suggest a significant decrease in protease-activity in patients treated with ORC/collagen compared with patients receiving control treatment, however, without affecting healing.[25,28,29]

In the 2000s, a sucrose octasulfate (technology lipido-colloid nano oligosaccharide factor; TLC-NOSF), was launched onto the market for the treatment of hard-to-heal wounds. The substance has been shown to inhibit excess MMPs and to stabilise growth factors.[25,30–32] The first clinical trial on this product was published in 2008 and demonstrated the superiority of TLC-NOSF dressings compared with ORC/collagen matrix dressings, in terms of VLU relative reduction after a 12-week treatment period.[33] Further supportive studies on different wound aetiologies followed.[30–32,34,35] Until 2016, these were the only two dressing types identified as MMP-inhibiting,[25,36] Since then, further products have come onto the market that promise an MMP-inhibiting effect, for example acetate mesh carriers containing potassium chloride, rubidium chloride, calcium chloride, zinc chloride, potassium citrate and citric acid.[37–41] This type of dressing is thought to inhibit MMP activity by altering the pH values in wounds,[37–41] Their beneficial impact on wound healing has been reported in patients with hard-to-heal wounds.[42–44]

There is no precise definition of dressings acting on protease activity.[45] For example, in the *Wound Care Handbook 2016* superabsorbent dressings are defined as

protease-modulating, however, the Royal Pharmaceutical Society does not categorise them as such.[46–48] For the purposes of this review, the authors distinguish between MMP-inhibiting and MMP-modulating wound dressings by defining MMP-inhibiting dressings to be those specifically marketed as having protease-altering activity, with this as a key feature of the product. In contrast, MMP-modulating dressings comprise all dressings altering the wound environment and thereby leading to changes in the concentrations or actions of proteases and are not considered in this review.

Aim

To date, diverse clinical studies on the use of MMP-inhibiting dressings for the treatment of hard-to-heal wounds of different aetiologies have been published.[11–14,19] As the current literature is lacking an overview of the different applications of these dressings as well as of the evidence for their efficacy in wound healing, the aim of this literature review is to provide an outline on the current state of knowledge in hard-to-heal wound treatment with MMP-inhibiting dressings. The question of whether MMP-inhibiting wound dressings are beneficial compared with other dressings based on current scientific evidence is addressed. Finally, recommendations regarding the use of MMP-inhibiting wound dressings in hard-to-heal wound treatment are made.

Methods

For the selection of relevant data, a search in literature- and clinical trial databases was carried out on 23 July 2019. To ensure the applicability in clinical practice, only databases freely available to health professionals were used. The search was specifically designed to identify publications assessing MMP-inhibiting wound dressings compared with any other wound dressing in wound healing. The following electronic bibliographic databases were screened to identify relevant publications: MEDLINE (PubMed) and CENTRAL (Cochrane library). In order to identify relevant randomised clinical trials (RCTs), the following clinical trial registers were searched: ClinicalTrials.gov, EU Clinical Trials Register and PharmNet.Bund as well as the International Clinical Trial Registry Platform Search Portal (ICTRP) of the World Health Organization (WHO).

Search strategy

The search strategy was initially developed for MEDLINE and then adapted to each of the databases. The following main keywords were used singularly and in various combinations: chronic wounds, MMP-inhibition, wound dressing, wound healing and wound size reduction. A complete list of all keywords, synonyms and MeSH Terms used is provided in Table 1.

Inclusion and exclusion criteria

Inclusion and exclusion criteria for study selection were determined by means of the PICOS (population, intervention, comparator, outcome, study type) scheme. The inclusion criteria were as follows: patients ≥18 years; patients with exudative hard-to-heal wounds; interventions containing MMP-inhibiting wound dressings as predefined by the authors of this review; any wound dressing as comparator; outcomes including wound size reduction or wound healing; RCTs; publication period between January 1998 and July 2019; publication language English, English full text available; study status finished with published results.

The exclusion criteria were as follows: patients <18 years; patients with tumour induced or fistula wounds with deep abscess; interventions other than MMP-inhibiting wound dressings; studies without a comparator; endpoints other than wound size reduction or healing; non-RCTs; publication period before 1998; publication languages other than English, no English full text available; study status still recruiting or no results published.

Data collection and analysis

Title and abstract screening of the studies identified was performed independently by two reviewers. In case of unambiguous results, full texts of these publications

Fig 1. Flow chart of study selection process. Literature search (23 July 2019)

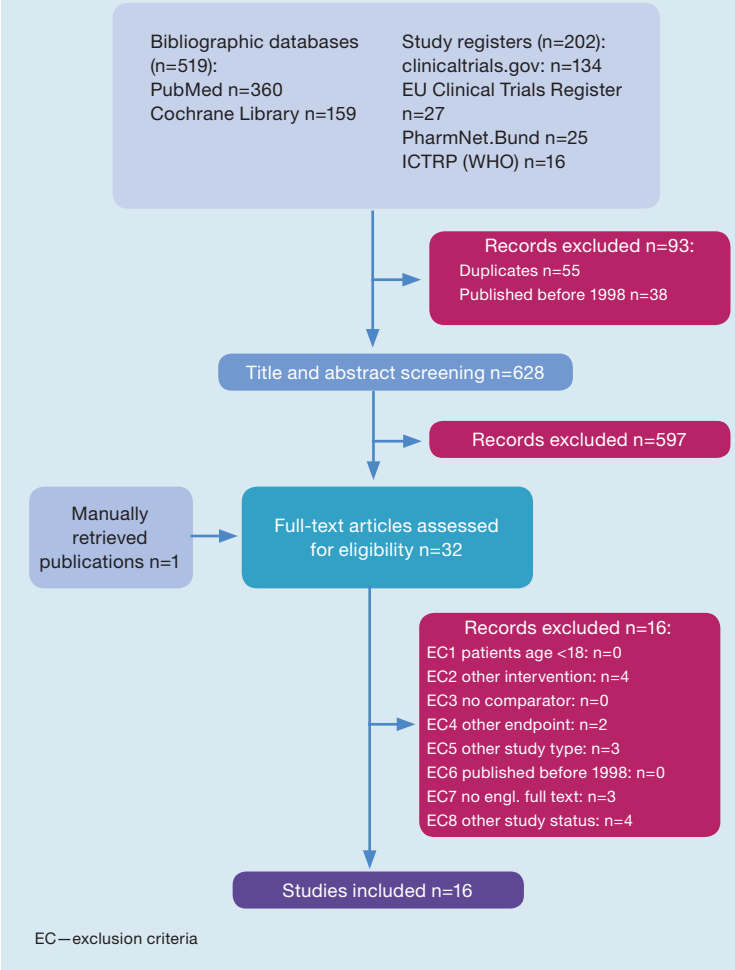

Table 2. Overview and description of randomised controlled trials (RCTs) included in the review

Quality level/ Authors	Study design/ population/ primary outcome	Total number randomised patients/ treatment versus comparator n (n/n)	Product	Comparator
High Edmonds et al. 2018[34]	■ DFU ■ Double blind ■ Adults ≥18 years) with non-infected neuro-ischaemic DFU >1cm², grade IC or IIC (University of Texas diabetic wound classification) Proportion of patients with wound closure at week 20	240 (126/114)	Sucrose octasulfate (URGOStart Contact, Laboratoires Urgo Medical, France)	Same dressing without sucrose octasulfate (UrgoTul, Laboratoires Urgo Medical, Chenôve, France)
Moderate Cullen et al. 2017[56]	■ VLU ■ Open label, multicenter ■ Adults (≥18 years) ■ Mean % wound size reduction after 12 weeks	49 (22/27)	Collagen-ORC-silver and SOC, defined as compression and AdapticTM (Acelity, San Antonio, Texas)	Standard of care
Moderate Donaghue et al. 1998[57]	■ DFU ■ Open label ■ Adults (≥21 years) with DFU ≥1cm² ■ Safety and efficacy of collagen-alginate as topic wound dressing	75 (50/25)	Collagen-alginate dressing FIBRACOL (Johnson & Johnson Medical, US)	Conventional treatment with saline-moistened gauze
Moderate Gottrup et al. 2013[58]	■ DFU ■ Multicentre ■ Adults (35-80 years) with DFU ≥30‘ days duration, no local or systemic signs of infection, Wagner grade 2-3 ■ 50% wound size reduction ■ Healing (100% re-epithelialisation)	39 (24/15)	Collagen-ORC-silver (Promogran Prisma, Systagenix Wound Management Limited, UK)	■ Foam dressing (Biatain, Coloplast, Humlebæk, Denmark) for moderately exuding wounds ■ Absorbent dressing (Mesorb, Mölnlycke Health Care, Gothenburg, Sweden) for exuding wounds
Moderate Kakagia et al. 2007[59]	■ DFU ■ Single centre ■ Adults (≥18 years) with diabetic ulcers ≥2.5cm² and ≥3 months duration ■ Ulcer dimension change within eight weeks	51 (17/17/17)	Promogran (Collagen-ORC, Johnson & Johnson)	2 comparators: ■ c1: autologous growth factors ■ c2: Promogran and growth factors

were assessed for eligibility. In general, disagreements between the reviewers were solved by discussion. All reasons for exclusion were documented.

Studies being reported in multiple publications or reviews were included only once. Nevertheless, in order to ensure that maximal relevant data were obtained, extraction was performed using all publications. A handsearch was performed in addition to the systematic search in bibliographical and clinical trial databases.

For methodological appraisal, relevant information extracted from the studies was summarised in tabular form for subsequent assessment. As recommended by the Centre for Reviews and Dissemination,[49] a table for the quality assessment of studies was included and adapted according to Rodgers et al.[50] Included studies were further assessed in an expert consensus to evaluate their quality on the basis of recognised standards.[51–53] Characteristics of high-quality were defined as studies with double-blinded design, cohort size >100 patients, study duration >8 weeks and the patient-relevant endpoint complete healing. Studies including ≥30 patients, a study duration of ≥8 weeks and reasonable publication bias were considered of moderate quality. All other studies were assessed as low quality studies. Studies were clustered according to their quality and are summarised in Table 2.

Study location/ study duration	Results	Strengths/ limitations
France, Germany, Italy, Spain, UK Run-in: 2 weeks, Treatment: 20 weeks	■ Wound closure (% of patients): 48 versus 30 (t versus c, 95% CI [5; 30]; adjusted OR 2.6, 95% CI, [1.43; 4.73]; p=0.002) ■ median time to wound closure (days): 120 (t, range 110–129) versus 180 (c, range 163–198), p=0.029 ■ median absolute wound area reduction at week 20 (cm^2): 1.8 (t, interquartile range 0.9–3.8) versus 1.2 (c, interquartile range 0.6–2.4), p=0.022	Strengths: ■ Compliant with proposed guidelines for study design and reporting ■ Computer-generated randomisation ■ Patients comply with daily clinical routine ■ Sensitivity analysis ■ Run-in-period to exclude patients with 'easy-healing' wounds ■ Protocol amendment to account for falsely high ABPI values
US 12 weeks	■ Mean wound size reduction after 12 weeks (%): 85.6±28.6 versus 72.5±77.8 (t versus c, n.s.) ■ Healing rates (%) after 4 weeks: 23 versus 11 (t versus c, n.s.) ■ Healing rates (%) after 12 weeks: 64 versus 59 (t versus. c, n.s.)	Strengths: ■ Detailed information on missing data ■ Comparable groups Limitations: ■ No run-in-phase to exclude easy healing wounds ■ Small cohort
n.a. 8 weeks	■ Mean wound size reduction (%) after eight weeks: 80.6±6 versus 61.1±26 (t vs. c, n.s.) ■ ≥75% wound size reduction (%): 78 versus 60 (t versus c, n.s.) ■ Complete healing (%): 48 versus 36 (t versus c, n.s.) ■ Mean time (weeks) to complete healing: 6.2±0.4 versus 5.8±0.4 (t versus c, n.s.) ■ Wound size reduction factoring in ulcer duration: in favor for collagen (p=0.0049)	Strengths: ■ ITT analyses ■ Detailed information on statistics ■ Standardised dressing changes Limitations: ■ Outcomes unclear defined ■ Missing data for study location ■ Small cohort
Denmark 14 weeks	■ 50% wound size reduction after four weeks (%): 79 versus 43 (t vs. c, p=0.035) ■ Complete healing (%): 52 versus 31 (t versus c, p>0.05)	Strengths: ■ Detailed information on study registration, randomisation ■ Standardised SOC Limitations: ■ Age range not consistent with inclusion criteria ■ Small cohort
Greece Run-in: ≥4 weeks, Treatment: 8 weeks	■ Wound length change (%): –18.59±10.36 versus –14.29±7.13 versus –33.76±14.74 (t versus c1 versus c2, p<0.001 in favour for c2) ■ Wound width change (%): –23.94±10.75 versus –17.41± 8.04 versus –46.06±13.06 (t versus c1 versus c2, p<0.001 in favour for c2) ■ Wound depth change (%): –35.59±10.64 versus –34.88±9.85 versus –55.12±10.83 (t versus c1 versus c2, p<0.001 in favour for c2) ■ No significant differences in ulcer dimension change between t and c1	Strengths: ■ Use of random number generator ■ Run-in-phase ■ Use of validated planimetry image tool Limitations: ■ Small sample size ■ Follow-up too short for full healing in most ulcers ■ Results not generalisable due to different quality of autologous growth factors delivered by gravitational platelet separation

Results

Study selection

Overall, the literature search yielded 721 hits with 519 publications identified in the bibliographic search (MEDLINE: 360 hits; CENTRAL: 159 hits) and further 202 hits identified by search in study registers (ClinicalTrials.gov: 134 hits; EU Clinical Trials Register: 27 hits; PharmNet.Bund: 25 hits; ICTRP: 16 hits). An overview of the literature search and selection process is given in Fig 1.

After removal of 55 duplicates and 38 hits published before 1998, 628 publications were further assessed. Out of the remaining records, 597 hits were excluded by title and abstract screening. The resulting 32 publications were thereafter assessed by full text screening, whereby 16 hits were excluded for various reasons (Fig 1).

We identified 15 publications in bibliographic databases,[28,29,33–35,54–63] and one publication was identified via handsearch.[64] Together, 1355 patients were examined in the included studies. In five studies, 681 patients with DFUs were enrolled.[34,57–59,63] In eight studies, 551 patients with VLUs,[28, 29,33,35,54–56,62] and in two studies 113 patients with PUs[60,61] were enrolled. In one further study 10 patients with hard-to-heal wounds of mixed origin were assessed.[64]

Due to the heterogeneity of the different studies in

Table 2. Overview and description of randomised controlled trials (RCTs) included in the review (continued)

Quality level/ Authors	Study design/ population/ primary outcome	Total number randomised patients/ treatment versus comparator n (n/n)	Product	Comparator
Moderate Meaume et al. 2012[35]	■ VLU ■ Double blind, multicentre ■ Adults (≥18 years) with noninfected VLU receiving effective compression therapy ■ Relative WAR (%)	187 (93/94)	Sucrose octasulfate (TLC-NOSF; URGO Start, Laboratoires Urgo Medical, Chenôve, France)	■ Same dressing without sucrose octasulfate (UrgoTul Absorb, Laboratoires Urgo Medical, Chenôve, France)
Moderate Romanelli et al. 2015[62]	■ VLU ■ Single centre ■ Adults with hard-to-heal VLU ■ Granulation tissue formation ■ Ulcer healing	40 (20/20)	Collagen membrane (ProHeal, MedSkin Solutions, Germany), non-adherent interface (Adaptic, Systagenix, UK), secondary dressing (alginate pad, Curasorb, Kendal, US)	■ Alginate pad (Curasorb, Kendal, US)
Moderate Schmutz et al. 2008[33]	■ VLU ■ Open label, two-armed, multicentre ■ Adults (≥18 years) with VLU 3–24 months duration, area 5–25 cm^2 ■ Wound relative reduction (% RR)	117 (57/60)	Sucrose octasulfate (TLC-NOSF; Laboratoires Urgo Medical, Chenôve, France)	■ Collagen-ORC (Promogran matrix, Johnson & Johnson, Ethicon)
Moderate Veves et al. 2002[63]	■ DFU ■ Open-label, multicentre ■ Adults (≥18 years) with ulcer area ≥1cm^2 ■ Complete healing after 12 weeks ■ Mean wound size reduction compared to baseline after 12 weeks ■ Mean time to complete healing	276 (138/138)	Promogran (Johnson & Johnson Wound Management, US)	■ Moistened gauze plus secondary dressing
Moderate Vin et al. 2002[29]	■ DFU ■ Open label, two-armed, parallel group design, multicentre ■ Adults (≥18 years) with stagnating VLU ■ Proportion of completely healed wounds ■ % wound size reduction from baseline	73 (37/36)	Promogran plus non-adherent dressing (Adaptic, Systagenix, UK), secondary gauze dressing	■ Promogran plus non-adherent dressing (Adaptic, Systagenix, UK), secondary gauze dressing

regard to indications and outcomes, a formal meta-analysis to evaluate the results of the included studies was not performed.

Literature search results

There were two different types of MMP-inhibiting dressings used in the identified studies. In 13 studies collagen-based dressings were tested either alone (n=9),[28, 29,54,55,59–63] in combination with silver (n=3)[56,58,64] or in combination with alginate (n=1).[57] There were three studies performed with TLC-NOSF-based wound dressings.[33–35]

The main focus of five studies was the efficacy of MMP-inhibiting wound dressings in the treatment of DFU.[34,57-59,63] In the majority (n=4) of these studies, collagen dressings were used in the treatment group,[57–59,63] in one study a TLC-NOSF-based dressing was investigated.[34] In 8/16 publications, data from patients with VLU were presented, mostly after treatment with collagen compared with any other dressing

Study location study duration	Results	Strengths limitations
France 8 weeks	■ Median WAR (%): –58.3 versus –31.6 (t versus c, 95% CI [–38.3; –15.1]; p=0.002)	Strengths: ■ Double-blind design ■ Computer-generated randomisation ■ Product and comparator identical except the addition of sucrose octasulfate in product Limitations: ■ Treatment duration too short to achieve complete wound healing in most patients
Italy Run-in: 6 weeks, treatment: 12 weeks	■ Granulation tissue formation increase (%) after 12 weeks 65 versus 38 (t versus c, p<0.001) ■ Wound area reduction (%): 45 versus 20 (t versus c, p<0.001) complete healing (n of patients): 6 versus 5 (t versus c, n.s.)	Strengths: ■ Run-in-phase ■ Exclusion of wounds improving during 6 weeks SOC ■ Standardised wound assessment Limitations: ■ No absolute numbers stated ■ Small cohort groups not compared regarding comorbidities
France, UK 12 weeks	■ % RR: PP population: 61.1 versus 7.7 (t versus c) with mean difference between groups ■ At last evaluation 33.6±15.0 in favour of t (95% CI [8.6%]) ITT population: median 54.4 versus 12.9 (t versus c, p=0.0286) ■ Wound area absolute reduction (cm^2) at last evaluation: 2.3±10.2 versus 0.2 ±10.4 (t versus c, p=0.01) ■ Healing rate (cm^2/day): –0.016±0.285 versus 0.075±0.475 (t versus c, p=0.029) ■ 40% wound area reduction (% of patients): in 56 versus 35 patients (t versus c, p=0.022) ■ Median healing time (days): 42 versus 84 (t versus c, p=0.06)	Strengths: ■ Good comparability of groups ■ Detailed information on statistical evaluation ■ Power calculation ■ ITT and PP analyses Limitation: ■ No detailed information on randomisation and allocation process available
US 12 weeks	■ Complete healing after 12 weeks (%): 37 versus 28.3 (t versus c, n.s.) subgroup wounds <6 months duration: 45.3 versus 32.6 (t versus c, p=0.056) subgroup wounds ■ 6 months duration: 18.6 versus 20.4 (t versus c, n.s.) ■ Mean wound size reduction compared to baseline after 12 weeks (%): 64.5 versus 63.8 (t versus c, n.s.) ■ Mean time to complete healing (weeks): 7.0±0.4 versus 5.8±0.4 ■ Subgroup wounds <6 months duration: 6.9±0.4	Strengths: ■ Study design reflects present clinical practice ■ Stratification on basis of wound size ■ Large sample size Limitation: ■ Allocation concealment unclear ■ Missing data on randomisation and blinding ■ No standardised offloading
France 12 weeks	■ Complete healing (% of patients): 41 versus 31 (t versus c, p=0.373) ■ Median wound area reduction from baseline (%): 82.4 versus 44.6 (t versus c, p<0.001)	Strength: ■ ITT analysis ■ Detailed information on dropouts Limitations: ■ Switch to another dressing allowed ■ High number of patients lost to follow-up

(n=6),[28,29,54–56,62] a TLC-NOSF-based dressing was used in two studies.[33,35] The effect of collagen-based wound dressings on PUs was discussed in two of the included studies.[60,61] Additionally, one collagen-study was conducted with patients of different wound entities.[64]

The patients-relevant outcome wound size reduction was analysed in 14 studies.[29,33–35,54–60,62–64] Furthermore, seven studies presented results on the number of patients with completely healed wounds.[29,34,57,58,61–63] Time to complete healing was investigated in four studies.[34,57,61,63] In general, healing times ranged from 14–129 days in the MMP-inhibitor groups and from 14–198 days in the comparator groups.[34,57,61,63] There were three studies that analysed healing rates.[28,33,56]

Within the performed literature research only one study[34] was identified as meeting the recognised standards of studies as defined in different recommendations and guidelines,[51–53,65,66] while nine

Table 2. Overview and description of randomised controlled trials (RCTs) included in the review (continued)

Quality level Authors	Study design/ population/ primary outcome	Total number randomised patients, treatment versus comparator N (n /n)	Product	Comparator
Low Bertone et al. 2009[55]	■ VLU ■ Single centre ■ Adults with hard-to-heal VLU of 6 weeks duration ■ N.a.	46 (n.a./n.a.)	Heterologous collagen (Condress, Abiogen Pharma, Italy) and compression	■ SOC with interface inert dressing and compression
Low Kloeters et al. 2016[60]	■ PU ■ Pilot study ■ adults (≥18 years) with pressure ulcers ■ 1cm^2 and 6 to <12 weeks duration ■ Elastase and plasmin activity in wound fluids ■ Healing rates	33 (23/10)	Collagen-ORC matrix and absorbing hydropolymer dressing (Tielle, Systagenix, UK)	■ Absorbing hydropolymer dressing (Tielle, Systagenix, UK)
Low Manizate et al. 2012[64]	■ Leg ulcers of mixed origin ■ Patients used as their own control (2 wounds of each patient) ■ Adults (≥18 y) with bilateral venous stasis or DFU ■ Wound size reduction	10 (10/10)	Sodium CMC, 1.2% ionic silver	■ Bovine native collagen (BDC)/ionic silver dressing
Low Nisi et al. 2005[61]	■ PU ■ Single centre ■ Adults (≥18 years) with pressure ulcers ■ Frequency of complete healing ■ Mean healing time	80 (40/40)	Protease-modulating matrix (Promogran, Johnson & Johnson, Ethicon) covered with hydropolymer	■ Viscose rayon gauze soaked in white vaseline covered with hydropolymer
Low **Smeets et al. 2008[28]**	■ VLU ■ Single centre ■ Adults (≥18 years) with VLU ■ MMP-2 concentration change during treatment ■ Gelatinase, elastase and plasmin activities in wound fluid during treatment ■ Healing rates	27 (17/10)	Collagen-ORC matrix, hydrocolloid secondary dressing	■ Hydrocolloid dressing

ABPI—ankle brachial pressure index; c—comparator; CI—confidence interval; CMC—carboxymethylcellulose; DFU—diabetic foot ulcer; ITT—intention to treat; n—number; n.
treatment; TLC-NOSF—technology lipido-colloid nano oligosaccharide factor; VLU—venous leg ulcers; WAR—wound area reduction

studies of moderate quality met the generally accepted criteria in most respects.[29,33,35,56–59,62,63]

Furthermore, six studies with major drawbacks regarding methodology and reporting of RCTs were classified as low quality.[28,54,55,60,61,64]

In general, all studies were industry sponsored, so that commercial interests cannot be excluded. A summary of the included publications in the order of their assessed rating is given in Table 2.

High-quality RCTs

The double-blinded RCT conducted on neuro-ischaemic DFUs was reported by Edmonds et al.[34] In this multicentre, double-blinded study with 240 patients, the analysis of the proportion of patients with wound closure after 20 weeks of TLC-NOSF treatment revealed a statistically significant difference in favour of the TLC-NOSF dressing compared with the same dressing without the MMP-inhibiting component TLC-NOSF (48% versus 30%; p=0.002). Furthermore, Kaplan-Meier-estimated time to wound closure was shorter with 120 (range: 110–129) days versus 180 (range: 163–198) days in the TLC-NOSF group (p=0.029). Selection or performance bias can be excluded due to the effective concealment and blinding by using dressings identical in appearance. Results of this well-conducted, large, long-term study

Study location study duration	Results	Strengths limitations
Italy Run-in: 3 weeks Treatment: 4 weeks	■ Median increase of wound bed granulation after 4 weeks (%): 65 versus 7 (t versus c, p<0.001) ■ Median reduction of relative ulcer area after 4 weeks (%): 50 versus 32 (t versus c, p<0.05)	Strengths: ■ Run-in-phase ■ Exclusion of patients with wound size reduction >50% Limitations: ■ Alternate allocation by investigator ■ Missing data on baseline characteristics and group sizes ■ Unclear endpoints ■ Small cohort ■ Short treatment period
N.a. 12 weeks	■ Wound area reduction after 12 weeks (%): 65±13 versus 41±11 (t versus c, p<0.05)	Limitations: ■ No detailed information on study location, blinding and randomisation available
US 8 weeks	■ Wound size reduction (cm^2/week): 0.79±0.735 versus 1.38±1.44 (t versus c, n.s.)	Strengths: ■ Good comparability Limitations: ■ Small cohort ■ Wounds of different origin
Italy Treatment: 18 months Follow-up: 6 months	■ Complete healing (% of patients): 90 versus 70 (t versus c, p=0.59) ■ Mean healing time (weeks): range 2-6 versus 2-8 (t versus c)	Strengths: ■ Long follow-up period Limitations: ■ No information on randomization, outcomes, baseline characteristics, statistics ■ Small cohort
N.a. 12 weeks	■ MMP-2 concentration change during treatment: n.s. ■ Healing rates during 12 weeks treatment: n.s.	Limitations: ■ No information on blinding, randomization, allocation available ■ No information on baseline characteristics available ■ No information on study location available ■ Small cohort

.a.—not applicable; n.s.—not significant; OR—odds ratio; ORC—oxidised regenerated cellulose; PP—per protocol; PU—pressure ulcers; SOC—standard of care; t—

support the use of TLC-NOSF dressing as a local treatment for neuro-ischaemic DFU.

Moderate-quality RCTs

The studies (n=9) listed alphabetically have in common a study duration of at least eight weeks and a cohort size of at least 30 patients. However, there are large qualitative differences so, all studies must be considered independently in order to evaluate the significance of the results.

Cullen et al. reported a study with 49 patients.[56] Treatment was performed with a combined collagen-silver dressing compared with standard of care (SOC). The primary outcome of this multicentre, open-label RCT was mean percentage wound size reduction of the treated VLU after 12 weeks of treatment. Additionally, healing rates after four and 12 weeks were investigated. Results show a trend towards an increased healing rate and shorter healing time in wounds treated with collagen-silver. Although the study's sample size resulted in an adequately powered study, data were not statistically significant. This might be due to the fact that no run-in-phase was performed to exclude easy healing wounds.

In an RCT with 75 patients with diabtes, randomised in a ratio 1:2, published by Donaghue et al., the efficacy of a collagen-alginate dressing was compared with conventional treatment with saline-moistened gauze.[57]

Differences in mean percenteage wound size reduction after eight weeks of treatment, complete healing rate as well as mean time to complete healing were not statistically significant between the groups. Study duration was probably too short to detect complete wound healing. Furthermore, treatment and control groups differed substantially in group size (50 versus 25 patients in the treatment and control group, respectively).

In the double-blinded RCT published by Gottrup et al., a cohort of 39 patients with Wagner grade 2–3 DFUs were treated either with a collagen-silver dressing plus SOC or SOC alone and followed for 14 weeks.[58] In 79% versus 43% of patients, 50% wound closure was observed by week four (p=0.035). More patients in the collagen-group compared with the control-group achieved complete healing, these results were statistically not significant (52 versus 31%; p>0.05). The study complies well with recognised standards of RCT reporting in terms of randomisation performance, blinding and the different aspects of wound care. However, the sample size is small and not based on an appropriate calculation of sample size and information on important baseline characteristics of study patients, such as diabetes type, are missing and impede the interpretation of the presented data.

Kakagia et al. reported a study designed to compare ORC/collagen dressing either versus autologous growth factors or in comparison with a combination of both treatments.[59] After a run-in-phase of four weeks,[51] patients with a DFU were randomly assigned in a ratio 1:1:1 to the treatment arms. DFU dimension changes were measured after eight weeks. The results for change in wound length, width and depth were statistically significant in favour of ORC/collagen plus growth factors (p<0.001 for all dimensions) as compared with autologous growth factors or ORC/collagen alone, as revealed by post-hoc analysis. However, study duration was too short to reach complete healing in most DFUs. Additionally, due to the varying quality of autologous growth factors delivered by gravitational platelet separation as well as the small cohort size (n=17 per group) and the lack of information concerning the baseline characteristics of the study population, the evidence of these results is in doubt.

A study with a TLC-NOSF dressing was performed by Meaume et al.[35] In this multicentre, double-blinded RCT comprising 187 patients with a VLU of 6–36 months' duration. Median wound area reduction (WAR) after eight weeks was reported for wounds treated with compression therapy and either a TLC-NOSF dressing or the same dressing without this component. Due to this study design, blinding bias could be excluded. Results revealed an advantage for the TLC-NOSF dressing compared with the dressing without TLC-NOSF (median WAR 58.3 versus 31.6%; p=0.002). The study was well conducted in relation to randomisation performance, blinding and the different aspects of wound care. Due to the relatively short study duration it remains uncertain how many patients may have reached complete wound healing.

In the RCT published by Romanelli et al., 40 patients with hard-to-heal VLUs were investigated.[62] Following a six-week run-in-phase, patients were randomised to receive either a collagen dressing or an alginate pad. After 12 weeks' treatment, wound size reduction and complete healing frequency were analysed. As a result, wound size reduction was greater using collagen compared with an alginate pad in 45% versus 20% (p<0.001) of cases. However, data for complete healing were comparable in both groups. Again, this study was conducted with a relatively small number of patients. Additionally, patients' baseline characteristics and blinding strategies were not sufficiently well described and patient groups were not compared regarding existing comorbidities.

The open-label study described by Schmutz et al. is the only one so far comparing two MMP-inhibiting wound dressings.[33] During a 12-week treatment, percentage wound relative reduction (%RR), wound absolute reduction (AR) and healing rate in 57 patients under TLC-NOSF and 60 patients under collagen treatment was measured. The superiority of the TLC-NOSF dressing could be demonstrated (median %RR 54.5 versus 12.9%; p=0.0286: AR 2.3±10.2 versus 0.2±10.4cm$^{2;}$ p=0.01: healing rate –0.016±0.285 versus 0.075±0.475cm^2/day; p=0.029). Additionally, 40% wound size reduction occurred in 56% versus 35% (p=0.022) of patients and was also clearly beneficial when wounds were treated with the TLC-NOSF-containing wound dressing compared with the collagen dressing. The study was performed according to recognised standards and it has to be noted that statistically significant results were obtained although recruitment was not completed. However, despite a blinded evaluation of wound area reduction, bias, due to the open-labelled study design, cannot be completely excluded.

The large, open-label multicentre study presented by Veves et al. with 276 enrolled patients revealed no statistically significant benefit of the collagen-based dressing as compared with standard treatment (saline-moistened gauze) in terms of complete healing after 12 weeks of treatment (treatment group 37.0% versus control group 28.3%) in patients presenting with a DFU.[63] Patients were further screened for the mean percentage wound size reduction as well as the mean healing time. In both groups of equally distributed patients, no statistically significant differences were detected between treatment and control groups. Results indicate that the collagen dressing used was comparable with saline-moistened gauze in terms of wound healing promotion in patients with DFUs receiving offloading. However, these results rest upon the data of less than 75% of the recruited participants. Furthermore, due to the lack of information on allocation concealment and randomisation, selection bias cannot be ruled out.

In the study reported by Vin et al., the objective was to evaluate the healing rates in VLU patients treated with a collagen-based dressing compared with a standard non-adherent dressing.[29] In this prospective, open-label study 37 patients with collagen treatment as well as

36 patients allocated to the control group were examined in terms of completely healed wounds and median percentage wound size reduction from baseline. While the number of completely healed wounds did not statistically significantly differ between groups, the median percentage wound size reduction from baseline was beneficial under collagen treatment (82.4 versus 44.6% in collagen versus control group, p<0.001). However, the investigated cohort was relatively small and a high number of patients was lost to follow-up. Furthermore, a high rate of treatment switches was recorded in the study.

Low-quality RCTs

Of the studies included in this review, six were characterised by very small cohorts, short study durations and/or a lack of essential information, such as characteristics of the study population and the investigated wounds, allocation concealment, endpoint definition and outcome assessment.[28,54,55,60,61,64]

Andriessen et al. investigated healing improvement in non-healing VLUs after treatment with either collagen, foam or paraffin gauze (n=4 per group).[54] The single-blinded pilot RCT was designed with a four-week run-in-phase followed by four weeks of treatment after a computer-generated allocation of patients. As a result, mean wound size reduction was improved in favour of the collagen dressing (31.8 versus 26 versus 17.2%), but results were statistically not significant. It has to be noted that data of studies with a very small sample size are not conclusive and generalisable.

In the RCT published by Bertone et al. comprising 46 patients, a median reduction of relative VLU size was reported to be statistically significant in favour of treatment with heterologous collagen compared with SOC (50 versus 32%; p<0.05) after four weeks.[55] However, the results of this study are in doubt, as the investigated cohort is relatively small with no information on group sizes and baseline characteristics, undefined endpoints as well as an extremely short treatment period.

Kloeters et al. studied 33 patients with PUs of 6–12 months' duration.[60] There were 23 patients randomly assigned to the treatment group with a collagen-based dressing, 10 patients were assigned to the control group receiving an absorbing hydropolymer dressing. Healing rates were measured after 12 weeks. With 65±13% versus 41±11%, healing rates were statistically significantly greater in wounds treated with collagen as compared with the control (p<0.05). However, the results of this pilot study is based on a small dataset with unequally distributed patient numbers (n=23 in treatment group versus n=10 in control group). Furthermore, information on allocation, randomisation and blinding are missing.

The use of a carboxymethyl cellulose (CMC)-silver dressing compared with a collagen-silver dressing was demonstrated by Manizate et al. in a small, open-label RCT. [64] There were 10 patients with bilateral venous stasis or DFUs who were enrolled and served as their own control. In this study, one wound per patient was treated with CMC-silver dressing, the second wound was treated with collagen-silver dressing. After eight weeks of treatment, wound size reduction was investigated, but revealed only minor differences between groups. Given the small number of investigated wounds (n=10 per group) the data are not conclusive or generalisable. Furthermore, investigated wounds were of different origin, further impairing the generalisability.

In the open-label study published by Nisi et al., patients with a PU were enrolled and randomly assigned in a ratio 1:1.[61] When comparing wounds treated with a collagen-based treatment versus wounds with viscose rayon gauze soaked with white vaseline in terms of complete healing frequency and mean healing time, no statistically significant differences were reported (90% versus 70%; p=0.59: 2–6 weeks versus 2–8 weeks, respectively). Due to missing data concerning patients' baseline characteristics, interventions and concomitant aspects of wound care, randomisation, statistics, and missing definitions on outcomes, the data of this study are not conclusive.

In an RCT described by Smeets et al., patients with VLUs were treated with a collagen-based dressing (n=17) and compared with wounds covered with a hydrocolloid dressing (n=10).[28] Healing during the 12-week treatment was detected and healing rates calculated. However, differences between study groups were statistically not significant. Due to the very small sample size, missing information on allocation, randomisation, blinding, and baseline characteristics, the results of this study cannot be interpreted.

Discussion

The treatment of patients presenting with hard-to-heal wounds requires precise diagnosis of the underlying cause and selection of suitable therapy regimes, based on high-quality research with reliable evidence. In this respect, RCTs are currently considered as the gold standard for investigating the effects of interventions. This also applies to the difficult field of hard-to-heal wounds, where there is a high burden on patients and, from a medical and economic perspective, on health authorities and payers. On the basis of pre-existing RCTs, this review examines the evidence base for MMP-inhibiting wound dressings that have been increasingly introduced to the market. Although guidance with regard to design and conduct of clinical trials as well as the reporting of data exists,[51–53,65] not all RCTs performed on MMP-inhibiting wound dressings are usable to derive conclusions appropriate for clinical practice. Studies differ in their quality and consequently in their strength of evidence based on their results. Furthermore, the reporting of studies is often inadequate, which complicates the assessment of study quality.

Evidence for the use of TLC-NOSF-based wound dressings

Results for dressings containing TLC-NOSF derived from three RCTs with high and moderate quality.[33–35]

Notably, the two double-blinded studies of Edmonds et al. and Meaume et al. set a high standard for the investigation of wound healing by using the same wound dressing with and without TLC-NOSF in identical packaging, thereby reducing bias.[34,35] Additionally, the patient groups were distinctly defined in these studies and the good as well as extensive study design made it possible to collect a great deal of data, which was published in other publications including cost-benefit and quality of life assessments.[67–69]

Results of the RCTs of Edmonds et al. and Meaume et al. are supported by a pooled analysis of non-comparative data from eight observational studies on the healing rates of hard-to-heal wounds in more than 10,000 patients with leg ulcers, DFUs and PUs.[70] NICE guidance also confirms the high level of evidence for beneficial effect of TLC-NOSF on wound healing in all types of DFUs and VLUs, and recommends this type of dressing as a treatment option for these diseases.[71] The current guidelines on the prevention and management of diabetic foot diseases of the International Working Group on the Diabetic Foot (IWGDF) recommends the use of TLC-NOSF-impregnated dressings in non-infected neuro-ischaemic ulcers without severe ischaemia among other treatments.[72] Furthermore, experts recommend, in a best practice recommendation for the implementation of a DFU treatment pathway in the UK, adding evidence-based local wound care to the standard of care in DFU treatment.[73] The relevance of using TLC-NOSF dressings in the treatment of VLUs has also been recognised in other publications.[25,36]

In the TLC-NOSF study of Schmutz et al., the superiority of this dressing against another MMP-inhibiting dressing was demonstrated. This indicates that differences in the efficacy on wound healing do not only exist between MMP-inhibiting dressings and other dressing types but also between different types of MMP-inhibiting dressings. However, this open-label study on patients with VLUs is the only study to date investigating the differences regarding the efficacy of hard-to-heal wound healing between TLC-NOSF and a collagen-based dressing. More studies on other indications would be desirable in order to confirm these results.

Evidence for the use of collagen-based wound dressings

Results of studies of collagen-based wound dressings are only of moderate or low-quality. Gottrup et al. showed statistically significant better results in favour of a collagen-silver dressing in patients with DFUs. The results for complete healing did not differ between groups. Other DFU studies revealed inconsistent results.[57,59,63] For example, Kakagia et al. reported statistically significant ulcer dimension changes only under treatment with collagen plus growth factors but not if collagen was used alone.[59] Considering the drawbacks of the mentioned studies, such as open-label study design, conducted without prior sample size calculation, small sample size or short study duration, the relevance of these data is questionable. Also, in a systematic literature review by Holmes et al. on the efficacy of collagen-based dressings for the treatment of DFUs, several limitations were identified in the analysed studies.[74] However, the authors still concluded that collagen-based dressings can be effective in the healing of DFUs. In contrast, Chicone et al. did not confirm this conclusion.[75] The authors conducted a meta-analysis on RCTs with ORC/collagen for the treatment of DFUs and concluded that due to several methodological flaws no evidence exists to suggest a beneficial effect of ORC/collagen on the wound healing rate of DFU as compared with SOC and point out the unmet need of higher-quality trials for the valid assessment of the efficacy of collagen-based dressings on the management of DFU.

Of the six studies focused on the efficacy of collagen-treatment on VLU healing,[28,29,54–56,62] three reported statistically significant results in favour of collagen for wound size reduction.[29,55,62] However, these results could not be confirmed in the other included studies. Furthermore, differences between the intervention and the control regarding complete healing or healing rates were not identified in any of the studies.[28,29,54,56,62] The same holds true for the RCT on mixed wound types.[64] Limitations of the mentioned studies, among others, were the open-label design with lack of blinded outcome assessments and of sample size calculations, small sample sizes as well as a high publication bias (insufficient information on baseline patient and wound characteristics, outcome definition, interventions, statistics), so that results do not allow any efficacy conclusions of collagen on VLU healing.

Also, in the current EWMA guidelines for the management of patients with VLUs, a criticism is that many studies on modern dressings are not powered for statistical significance, are unblinded for outcome assessment or include a highly selective population.[36] They note that evidence of efficacy exists only for some of the modern dressings that affect MMP activity. The lack of high-quality RCTs was also addressed by two other reviews.[45,47] Firstly, in a network meta-analysis of 59 studies dating from 1985 to 2016 on dressings and topical agents for treating VLUs, Norman et al. compared the effect of different dressings in terms of complete healing.[47] The authors considered many of the studies included to be at high risk of bias. Secondly, Westby et al., in 2016, investigated the effects of protease-activity altering dressings on the healing of VLUs by reviewing relevant RCTs.[45] The authors estimated the evidence for a positive influence on VLU healing relative to control dressings without effect on protease activity as low, primarily due to the risk of bias identified in most of the underlying studies of the meta-analysis.

In addition to the DFU and VLU studies, the present review also included two studies on PUs.[60,61] Due to shortcomings in the study design and reporting of data, the results have a low impact.[61] Similarly, in the literature review of Westby et al., investigating the probability of

complete PU healing associated with different dressings and topical agents, the authors found that results of the studies identified had a high imprecision in the evidence as well as high risk of bias.[5] Therefore, they judged the vast majority of evidence to be of low or very low certainty.

Use of MMP-inhibiting wound dressings in clinical practice

Results of several studies demonstrate a clear trend towards shorter healing times, if an earlier treatment with MMP-inhibiting dressings was initiated.[35,67,70] In this context, the use of TLC-NOSF dressings is indicated for hard-to-heal wounds such as DFUs and VLUs, as also recognised by health technology institutions and international working groups.[4,71,73] No recommendation is given by these institutions for collagen-based wound dressings.

Limitations of the present review

Potential bias in the review process may affect the publication language. Only studies containing an English full text were included, all other publications were ultimately excluded. It cannot be ruled out that informative data were missed due to this restriction. Furthermore, bias is possible due to the lack of screened databases, such as EMBASE and CINAHL. However, the present review focused in particular on freely accessible databases, which are available to a broad readership. To avoid bias, handsearch and reference check in reviews was performed and revealed only one additional hit. Furthermore, a search in clinical trial registers was performed. Therefore, it is unlikely that relevant results-affecting data are missing. Since only RCTs were included in the evaluation, a lack of evidence due to missing information from trials of clinical routine, such as in observational studies, cannot be excluded. However, the restriction to RCTs—representing the gold standard of clinical trials—with a generally high evidence class meant that a certain comparability of the evidence could be achieved.

Conclusion

This review article has considered available clinical data from MMP-inhibiting dressings, the ORC/collagen and the TLC-NOSF dressings. For the outcomes, wound size reduction and complete healing, significant evidence for the efficacy of TLC-NOSF wound dressings for DFUs and VLUs was identified. Therefore, the treatment of these wounds with TLC-NOSF is highly recommended. However, more high-quality, long-term studies are desirable to monitor the course of healing, for example for non-venous ulcers and other indications. Additionally, there is currently only limited evidence to support the use of collagen-based dressings in the treatment of hard-to-heal wounds. Hence, more RCTs meeting the required methodological and reporting standards are necessary to generate reliable results.

The main reason for the differences in evidence for the use of TLC-NOSF and collagen-based wound dressings are the differences in quality of the identified studies. Furthermore, inhibiting MMPs is probably only one of many different mechanisms, which improve the healing process of hard-to-heal wounds. The heterogeneity of the clinical outcomes of MMP-inhibiting dressings supports that other mechanisms are involved, which may explain these different clinical benefits. **JWC**

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Reflective questions

- What are the important mechanisms that make the difference between acute undisturbed wound healing and hard-to-heal wounds?
- What is the central therapeutic approach of the sucrose-octasulfate dressing in supporting wound healing?
- Which dressing is recommended by the International Working Group on the Diabetic Foot as the first-line therapy for non-infected neuro-ischaemic ulcers without severe ischaemia? Why?

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