

A Systematic Review of clinical efficacy of Protease-Modulating interventions with Diabetic Foot Ulcer or Venous Leg Ulcer

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Objective

To determine if protease modulating treatments are a clinically effective treatment strategy for Diabetic Foot Ulcers or Leg Ulcers.

Wound dressings

Wound dressings are a mainstay of treatment; being applied to a wound as part of a wider treatment strategy, guidelines include compression, debridement, offloading and infection control to achieve full wound closure^{1,2}.

Protease-modulating-matrix (PMM) dressings have an effect on the matrix-metalloproteases (MMPs) that are present in chronic wounds. These interventions are intended to rebalance the levels of MMPs in the wound bed, stimulating healing and improving outcomes.

Methods

A systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines was undertaken. This included a database search, and consultation with experts and manufacturers to identify additional literature.

Databases searched: Centre Reviews and Dissemination (CRD) York Database, Cochrane Library, Medline (PubMed), National Institute for Health and Clinical Excellence Evidence Search, Science Direct/Scopus.

Two researchers performed data extraction with a third consulted in case of discrepancies. A narrative synthesis of results and critical appraisal of included studies as per the NICE submission template for Medical Technologies Evaluation Programme; which has been derived from the Centre for Reviews and Dissemination (CRD) was performed.

Table 1. Inclusion/Exclusion Criteria

Inclusion criteria	
Population	Diabetic Foot Ulcer, Venous Leg Ulcer
Interventions	Protease Matrix Modulating dressings and topical applications
Outcomes	Wound Area Reduction (WAR), Wound Closure,
Study design	Randomised Controlled Trials, Observational studies
Language	English Language
Search dates	Search was carried out December 2017, date unrestricted.
Exclusion criteria	
Population	Paediatrics (<18), Acute wounds
Interventions	Surgical. Novel-non-surgical. Infection control. Debridement. Bioengineered skin substitute. Offloading. Prevention.
Outcomes	Not meeting inclusion criteria
Study design	In vitro studies, review or discussion articles, Treatment pathway/guidelines, Systematic/ Literature Reviews or Meta analyses, Epidemiology Studies, Modelling, Case Studies, Economic studies, Database Studies
Language	Non-English language
Search dates	Unrestricted

Uncertainty and new evidence

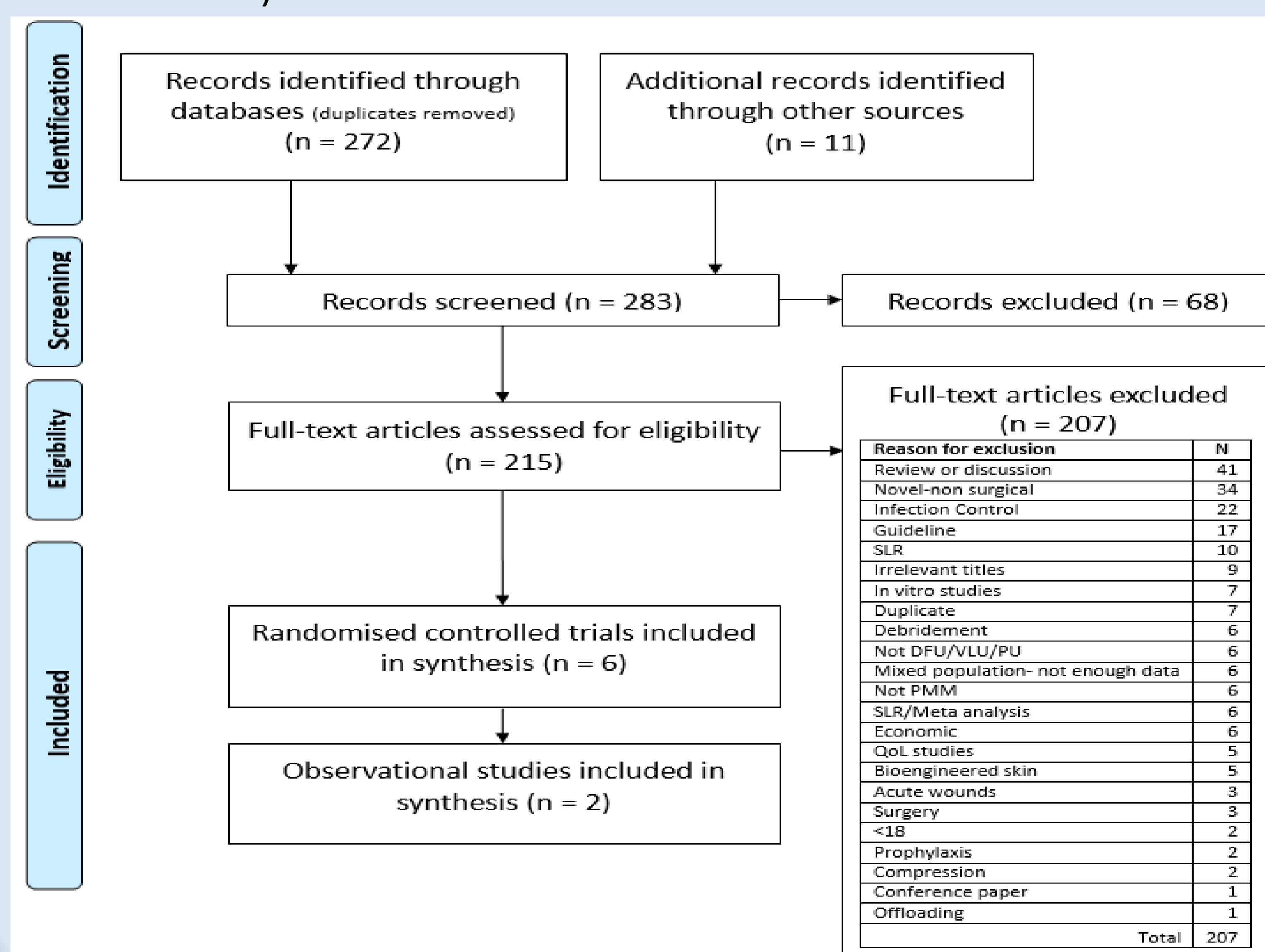
Advice from the National Institute for Health and Care Excellence (NICE) recommends "the least costly dressing of the type that meets the required characteristics appropriate for the type of wound"³.

A prior systematic review of PMM dressings did not find conclusive evidence of clinical benefit for Venous Leg Ulcers⁴. However newer studies have now been published; a pooled analysis⁵ and a Double-Blind Randomised Clinical Trial⁶ showing superior outcomes for PMM dressings. This has highlighted the need for a review of the evidence.

Results

From searching the databases 272 results were returned. Discussion with Experts and Manufacturers provided 11 further titles. After initial screening of the 283 titles and abstracts, 68 were excluded for being irrelevant. The remaining 215 texts were judged against the inclusion and exclusion criteria. 202 titles were excluded, with 8 being included as per the PRISMA flow chart.

Of the studies included, 3 had a primary outcome of relative WAR and 5 assessed healing or closure outcomes. Edmonds 2018 demonstrates an odds ratio of 2.6 (p=0.002) of healing at 20 weeks when using a PMM dressing on a DFU⁵. Looking at the total population Munter shows a 30.8% benefit when a treatment regime included the Protease Modulating Dressing, presenting as a 29.8% (CI: 28.8%-30.9%) benefit for LU patients and 37.4% (CI: 34.8%-40.1%) for DFUs⁶.



Conclusions

This study found evidence of protease-modulating interventions being clinically effective in the management of DFU and VLU. Two studies compare two wound care products by the same manufacturer, achieving double-blinding by producing both the intervention and control dressing with the same material, packaging and colours as one another; with the sole difference being the addition of the PMM agent^{5,7}.

The critical review of the evidence scored the RCTs as being of an overall moderate quality. The observational studies both scored as being of poor quality. This uncertainty of evidence means that more work is required to produce further evidence. Expert opinion in conjunction with data from clinical studies and literature could inform better treatment practices.

This systematic review highlights the need for further research into the efficacy of protease-modulating treatments. They have been shown to have some efficacy; with the dressing preparation being particularly beneficial to ulcers that are older and larger; which are often the most burdensome ulcers.

The findings of this systematic review could be used to inform clinical decision making with regards to PMM interventions. These interventions are more costly than basic alternatives; however this review has shown that they may improve healing outcomes for patients; with enhanced potential in patients with DFU and on older and larger wounds.

References:

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4. Westby, M., Norman, G., Dumville, J., Stubbs, N. and Cullum, N. Protease-modulating matrix treatments for healing venous leg ulcers. *Cochrane Database of Systematic Reviews*. 2016; 12. Article: CD011918.
5. Munter, K. et al., 2017. The reality of routine practice: a pooled data analysis on chronic wounds treated with TLC-NOSF wound dressings. *Journal of Wound Care*, Volume 26, pp. 4-15.
6. Edmonds, M. et al., 2018. Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. *The Lancet Diabetes & Endocrinology*, Volume 6, pp. 186-96.
7. Meaume, S. et al., 2012. A randomized, controlled, double-blind prospective trial with a Lipido-Colloid Technology-Nano-OligoSaccharide Factor wound dressing in the local management of venous leg ulcers. *Wound Repair and Regeneration*, 20(4), pp. 500-11.