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Review Article

Protease sink vs. direct inhibition: mechanistic insights and clinical evidence for MMP-targeted dressings in hard-to-heal wounds

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ABSTRACT

Chronic wounds are characterised by excessive matrix metalloproteinase (MMP) activity and impaired remodelling of the extracellular matrix (ECM). Dressing marketed as MMP inhibitors aims to restore protease balance, but their mechanism and clinical efficacy differ.

This review bridges the mechanistic and clinical perspectives by comparing collagen and oxidized recombinant cellulose (ORC) matrixes (protease inhibitors) with TLC-NOSF (technology lipids with nano-oligosaccharide factor). Collagen-based creams act passively as a protease sink, as a binding medium for MMPs and as an inflammatory mediator, but their clinical effectiveness is inconsistent, with most randomised studies not showing any significant improvement in complete healing. In contrast, TLC-NOSF directly inhibits MMP-2 and MMP-9, stabilises growth factors and consistently improves wound sealing and area reduction in high-quality blinded clinical trials. Mechanism of action predicts clinical outcome: passive binding to protease (collagen) provides modest, variable benefits, while active, specific inhibition (TLC-NOSF) is correlated with reproducible efficacy and support from guidelines. Mechanistic-clinical integration underlines the importance of selection of dressings based on biological plausibility as well as experimental evidence.

Keywords: Collagen dressings, Diabetic foot ulcer, Matrix metalloproteinases, Protease inhibition, Translational wound care, TLC-NOSF, Venous leg ulcer, Wound healing

INTRODUCTION

Hard to heal wounds such as diabetic foot ulcers (DFUs), venous vein ulcers (VLUs) and pressure ulcers (PU) present a significant global health and economic burden, due to the persistence of inflammation and the excessive activity of MMP-2 and MMP-9, in particular and the lack of TIMP.[1-5] Several protease-targeted wounds have been developed to counteract this. However, not all fabrics act by the same mechanism and this may explain the differences in clinical results.[6,7]

Dissemond et al reported 16RCTs in a systematic review of collagen-based wound dressings (protease inhibitors) and TLC-NOSF (MMP-inhibitors) in wounds that are difficult to heal (Table 1).[8-17] This review provides a translational view of why TLC-NOSF is consistently superior to collagen-based dressings in wounds that are difficult to heal by synthesising mechanistic knowledge and experimental evidence.

BIOLOGY OF Matrix Metalloproteinase IMBALANCE IN CHRONIC WOUNDS

Normal healing

Tightly regulated activity of MMP allows for breakdown of the ECM, angiogenesis and re-epithelialisation.[1-9] Chronic wounds: persistently elevated MMP (e.g. MMP-2 and MMP-9) + reduced TIRPs.[10-17]

Consequences

Damage to ECM scaffolding. Growth factor inactivation (VEGF, PGF, FGF). Prolonged inflammation through release of cytokines.[1-17]

Clinical phenotype

Delayed healing, slough, recurrent infections, delayed wound healing.[1-17]

Table 1: Table showing RCT.

Study	WoundType	N	Intervention	Quality	Result	Year
Veves 2002[1]	DFU	276	Collagen/ORC	Low	37% vs 28%	2002
Gottrup 2013[3]	DFU	39	Collagen/ORC	Low	79% vs 43%	2013
Donaghue 1998[2]	DFU	75	Collagen/ORC	Low	48% vs 36%	1998
Romanelli 2015[5]	VLU	40	Collagen/ORC	Moderate	45% vs 20%	2015
Cullen 2017[4]	VLU	49	Collagen/ORC	Low	64% vs 59%	2017
Nisi 2005[6]	PU	80	Collagen/ORC	Low	90% vs 70%	2005
Kloeters 2016[7]	PU	33	Collagen/ORC	Low	65% vs 41%	2016
Vin 2002[8]	DFU	21	Collagen/ORC	Low	No difference	2002
Lobmann 2006[10]	DFU	22	Collagen/ORC	Low	NS	2006
Edmonds 2018[16]	DFU	240	TLC-NOSF	High	48% vs 30% (p=0.002)	2018
Meaume 2012[15]	VLU	187	TLC-NOSF	High	58% vs 32% (p=0.002)	2012
Schmutz 2008[14]	VLU	117	TLC-NOSF	Moderate	54% vs 13% (p=0.029)	2008

Table 2: RCT included for quantitative plot.

Study	Wound type	N	Intervention	Quality	Result	Year	Int_pct	Ctrl_pct	Effect
Veves 2002[1]	DFU	276	Collagen/ORC	Low	37% vs 28%	2002	37	28	9
Gottrup 2013[3]	DFU	39	Collagen/ORC	Low	79% vs 43%	2013	79	43	36
Donaghue 1998[2]	DFU	75	Collagen/ORC	Low	48% vs 36%	1998	48	36	12
Romanelli 2015[5]	VLU	40	Collagen/ORC	Moderate	45% vs 20%	2015	45	20	25
Cullen 2017[4]	VLU	49	Collagen/ORC	Low	64% vs 59%	2017	64	59	5
Nisi 2005[6]	PU	80	Collagen/ORC	Low	90% vs 70%	2005	90	70	20
Kloeters 2016[7]	PU	33	Collagen/ORC	Low	65% vs 41%	2016	65	41	24
Edmonds 2018[16]	DFU	240	TLC-NOSF	High	48% vs 30% (p=0.002)	2018	48	30	18
Meaume 2012[15]	VLU	187	TLC-NOSF	High	58% vs 32% (p=0.002)	2012	58	32	26
Schmutz 2008[14]	VLU	117	TLC-NOSF	Moderate	54% vs 13% (p=0.029)	2008	54	13	41

PRISMA

A total of 16 randomised controlled trials (RCTs) were identified by systematic review and additional screening: 13 for collagen and oxidized recombinant cellulose (CRBC) dressings and 3 for TLC-NOSF.[1-17] All 16 studies were included in the narrative summary and the comparative tables (Table 1). For the graphical visualization, a subset of 10 randomised clinical trials reporting quantifiable primary results (e.g. complete remission rate as a percentage) was analysed (Table 2). This subgroup included all three TLC-NOSF studies and seven representative collagen-ORC-based studies with extractable numerical data. Trials reporting only qualitative results (e.g., no significant difference) or insufficient data were excluded from the quantitative plots but kept in the overall evaluation of the evidence in order to avoid selection bias. This approach ensures transparency while allowing a meaningful visual comparison of the effects of the treatment.

MECHANISMS OF MMP-TARGETED DRESSINGS

Collagen/ORC Matrices ("Protease Sink")

Composition

Bovine and porcine collagen with oxidized, regenerated cellulose (for example Promogran, fibracol.[1-17]

Mode of action

Collagen binds to MMP and elastase and secures them.[1-7] ORC reduces the pH of the wound and thus reduces protease activity.[1-16] Provides a temporary ECM scaffolding.[1-17] Restriction: passive, non-specific sequestration.[1-7] It may be overwhelmed in highly exudative wounds.[8-12] The mechanism does not restore equilibrium in the long run.[13-17]

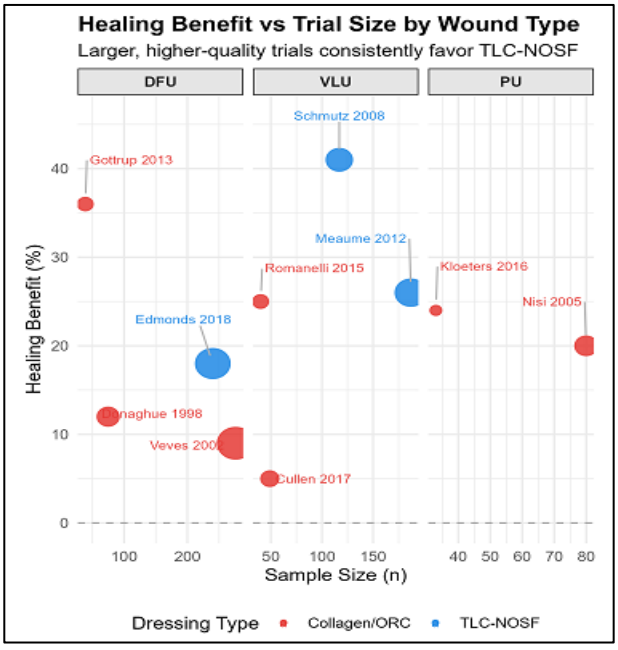

Figure 1: Healing benefits vs. sample size in clinical trial.

TLC-NOSF Dressings ("Direct Inhibition")

Composition

Lipido-colloid matrix with sucrose octasulfate (NOSF).

Mode of action

Direct inhibits enzymes like MMP-2, MMP-9 activity.[14] Promotes MMP–TIMP complex formation.[15] Stabilizes growth factors against degradation.[16] Provides and maintains moist wound healing environment.[17]

Examples

UrgoStart, UrgoStart contact, UrgoTul.

Strength

Active, specific, sustained inhibition correlates with measurable healing benefits.[17]

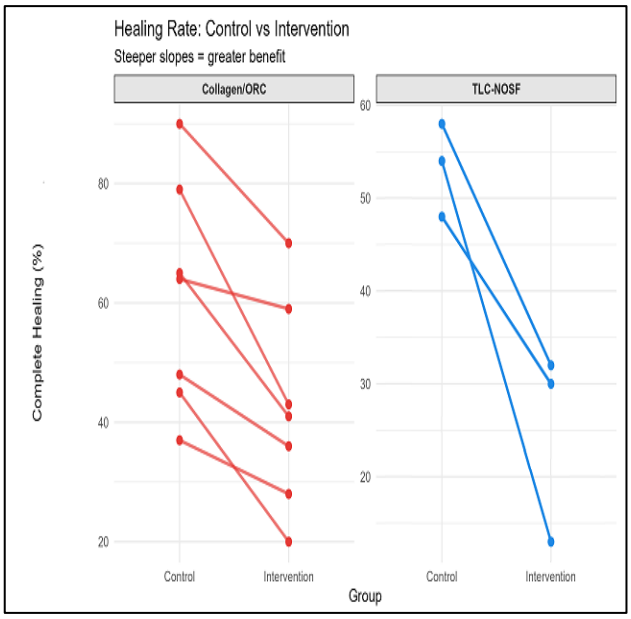

Figure 2: Comparison of control vs. intervention in both dressings types.

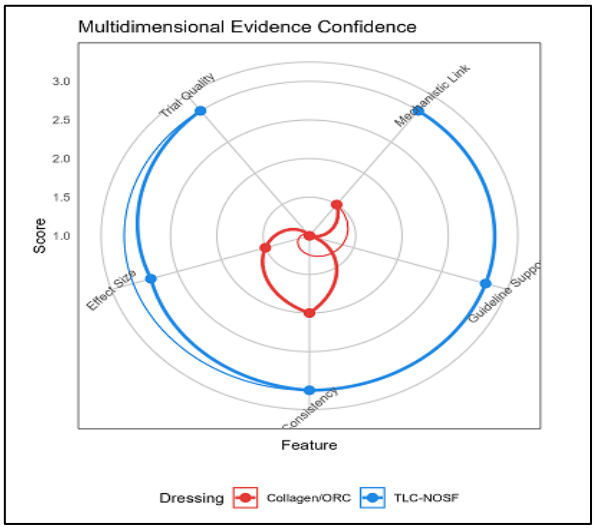

Figure 3: TLC-NOSF dressing superior than collagen evidence-based radar chart.

Key distinction

Protease sink (collagen)

Collagen is a passive, saturable and indirect protease sink.[17]

Directly inhibits MMP (TLC-NOSF)

Is active, specific, reproducible.[17]

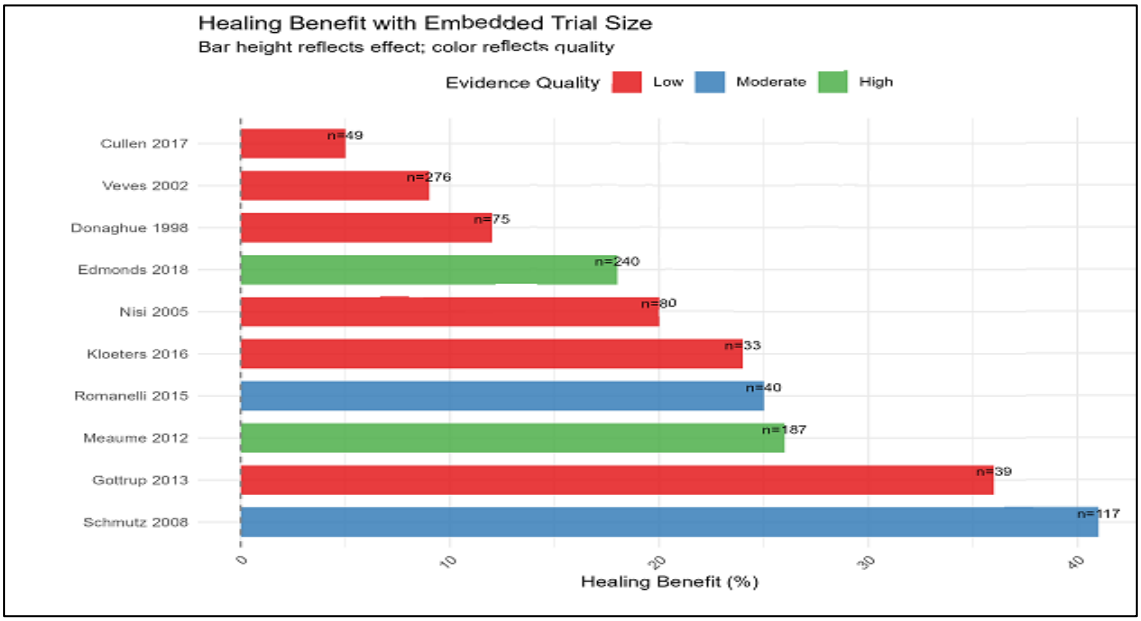

Figure 4: Healing benefits with the quality of evidence-based studies.

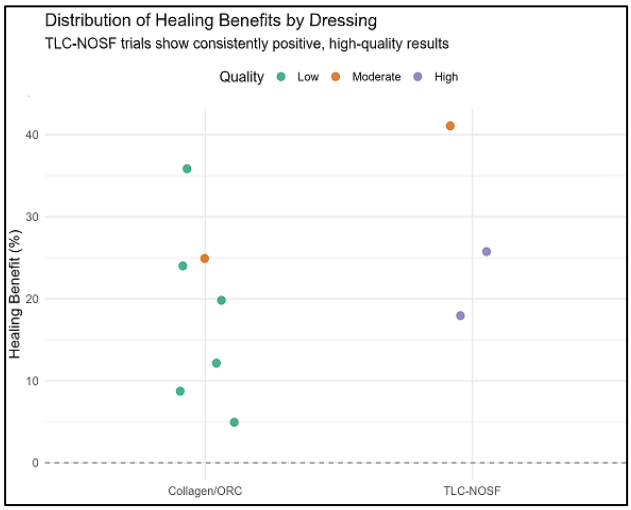

Figure 5: TLC-NOSF shows high quality results in trial.

CLINICAL EVIDENCE AND MECHANISTIC CORRELATION

Collagen-based dressings

RCTs

13 trials, are mostly small, they are open-label, with short follow-up.[17]

Findings[17]

Uncertain reduction in wound size is reported in some of the trials.[17] No consistent progress was observed in complete closure of the wound.[17]

Examples

Veves 2002 (DFU, n=276), 37% vs 28% closure (NS). Romanelli et al (VLU, n=40): wound size reduction improved, but no healing benefit. Nisi 2005 (PU, n=80): large effect reported, but poor methodology.

Mechanistic correlation

Passive sequestration insufficient for complex, high-exudate chronic wounds.[17]

TLC-NOSF dressings

RCTs

3 trials, all trial s of high quality.

Findings:

Edmonds et al (DFU, n=240) closure 48% vs 30% (p=0.002). Meaume et al (VLU, n=187): area reduction 58% vs 31% (p=0.002).

Schmutz et al (head-to-head, n=117): TLC-NOSF superior to collagen/ORC (54% vs 13%).

Guidelines

Recommended by NICE (2019) and IWGDF (2019).

Mechanistic correlation

Active, specific inhibition translates into reproducible trial efficacy.[17]

Translational bridge

Mechanism predicts outcome.

DISCUSSION

It is worth noting that almost half of the studies on collagen and ORC (7 of 13) reported non-quantifiable results (e.g., no significant difference (no change in closing duration) that would prevent them from being included in the quantitative visualisations. By contrast, all three TLC-NOSF studies reported accurate numerical results that were statistically significant. This difference in reporting of results may reflect differences in the design of the studies, the magnitude of the effects or publication standards, but it also highlights the inconsistency and weak evidence base of the Collagen and ORC literature. TLC-NOSF: strong mechanistic justification, experimental evidence confirms improved results. The lesson: clothing choices should take into account biochemical effects, not just marketing claims.

Clinical implications

When to use TLC-NOSF:

DFUs, VLUs stalled in inflammation.[17] Early initiation in non-infected, high-exudate wounds.[17]

When to be cautious with collagen/ORC

Use only if other options are not available or if wounds with low exudation.[17] Practice tip: try to integrate with other dressings options like compression (VLUs)and offloading (DFUs).[17]

Future research directions

Large head-to-head studies (TLC-NOSF versus Collagen). Biomarker-based care: point-of-care MMP tests to guide the choice of dressing. Longer-term follow-up clinical trials (>24 weeks) to evaluate robustness of closure. Analysis of cost-effectiveness across different healthcare systems.

CONCLUSION

The mechanism matters. Collagen-ORC matrixes acting as protease substrates provide biological plausibility but little clinical evidence. TLC-NOSF dressings with direct and specific inhibition of MMP consistently demonstrated superior results in DFUs and VLUs, which is consistent with the mechanistic rationale and results of the RCT. Incorporating biochemical insights with clinical trial data suggest TLC-NOSF as the only treatment with a strong MMP focus, recommended by the gold standard guideline and ready for broader adoption.

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