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Elevated levels of matrix metalloproteinases and chronic wound healing: an updated review of clinical evidence

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Elevated levels of matrix metalloproteinases and chronic wound healing: an updated review of clinical evidence

• **Objective:** In the past 20 years, research and clinical trials on the healing process of chronic wounds have highlighted the key role of the family of enzymes called matrix metalloproteinases (MMPs). If a strong correlation between the course of healing of chronic wounds and the levels of a biological marker can be demonstrated, then it may be possible to: i) identify the best marker threshold to predict the clinical evolution of the pathology; and ii) if causality has been found between the marker and pathology, to improve the healing outcome, to change the marker level.

• **Method:** The databases Medline and Embase were searched to identify clinical trials pertaining to the assessment of MMPs in chronic wounds with the following keywords 'metalloproteinase' or 'metalloprotease' and 'wound healing'. Clinical trials were considered for inclusion if they enrolled patients with cutaneous chronic wounds and were published in English. More than 50 clinical trials, consensus documents and guidelines were assessed for this review.

• **Results:** MMPs play key roles in the wound healing process, and excessive expression and activation of some of these enzymes is seen in chronic cutaneous wounds where healing is delayed. Levels of MMPs are affected by a number of factors, including patient and wound characteristics.

• **Conclusion:** Levels of MMPs can be used to indicate the prognosis of chronic wounds and protease modulating treatments used to improve healing rates.

• **Declaration of interest:** The authors report no conflicts of interest in this work.

matrix metalloproteinase; chronic wound; wound healing

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In the past 20 years, clinical trials and other research on the healing process of chronic wounds have highlighted the key role of a family of enzymes, matrix metalloproteinases (MMPs). An increasing number of articles have been published on this subject. Here we aim to offer a global and updated review of the clinical evidence published up to 2015.

After introducing the issue of wound chronicity and examining possible causes of delayed healing, including the MMP families, we will examine some questions regarding this subject, the methodology used in this review and the answers given by the scientific literature.

Chronic wounds and healing rates

Chronic wounds are defined as wounds where healing is delayed due to one or more factors. Depending on the aetiology, a wound is considered to be chronic if it is still present after four to six weeks.[1] Such wounds may from the outset show chronic features, for example leg ulcers, pressure ulcers (PUs), diabetic foot ulcers (DFUs) and amputation stumps, or may initially be acute in nature (such as surgical wounds and traumatic wounds) and become chronic after several weeks of stagnation due to the patient's general condition or inappropriate care; they may last for several months or years.[2,3] Even if care follows the recommended best practice set out in guidelines for each aetiology, chronic wound closure needs a considerable amount of time and, in some case, may never occur.

In patients with venous leg ulcers (VLUs), despite similar disease patterns and treatment, there is great variation in clinical outcome. In a 2007 study on the cost of treating wounds in the UK, 42% of patients with a leg or foot ulcer had had the wound for more than six months, and 27.5% for more than one year.[2] These results corroborated those of another study in which it was reported that 19–37% of leg ulcers had been present for more than two years.[3]

Similar observations have been made in groups of patients with DFUs. Healing rates with standard treatments for chronic DFUs are slow, averaging 12–20 weeks in clinical trials.[4] In a meta-analysis of five prospective DFU trials, Margolis et al. reported a global healing rate of 24% after 12 weeks and 33% after 20 weeks of standard treatment.[5] This means that, after 20 weeks of standard treatment, approximately 70% of DFUs remain unhealed.

In this context, follow-up duration is usually an important constraint for clinical trials assessing

wound closure in chronic wounds. However, numerous publications have shown that the initial change in wound area is highly predictive of a complete healing,[6–11] and some authors consider that the relative wound area reduction (RWAR) at week 4 might be considered as a surrogate endpoint to complete closure. It has been established that:

- VLU RWAR ≥40% at week 4 is predictive of complete closure within 24 weeks[6]
- DFU RWAR ≥50% at week 4 is predictive of complete closure within 12 weeks.[7,10,11]

Either way, regardless of the clinical outcome selected (wound closure at week 12 or RWAR at week 4), clinical trials assessing the management of chronic wounds commonly report that a considerable proportion of wounds have a poor outcome.[5,6,11,12]

Table 1. The main MMPs involved into the wound healing process

Type of MMPs	Sub group of MMPs	Denominations
Soluble gelatinases	Gelatinases	MMP-2: Gelatinase-A MMP-9: Gelatinase-B
Archetypal MMPs	Collagenases	MMP-1: Collagenase-1, Interstitial collagenase MMP-8, Collagenase-2, Neutrophil collagenase MMP-13: Collagenase-3
	Metalloelastase	MMP-12
	Stromelysins	MMP-3: Stromelysin-1 MMP-10: Stromelysin-2 MMP-11: Stromelysin-3
Matrilysins	Matrilysins	MMP-7: Matrilysin MMP-26: Matrilysin-2

MMP–Matrix metalloproteinase

Impaired wound healing factors and chronic wound genesis

Factors that may affect the healing status and complexity of wounds are regularly updated.[13–18] Among these are ulcer chronicity or wound surface, arterial or venous deficiency, patient age, inadequate nutrition and infection. All of these factors should be taken into account when assessing chronic wounds, some of them, such as ischaemia, hypertension or hyperglycaemia, might be linked more to the fundamental mechanisms leading to the genesis of the wound itself.[16,18]

Chronic wounds are usually characterised by multiple physiologic and biochemical defects, known to lead to impairment of the normal wound healing process. Prolonged inflammation, deleterious degradation:synthesis ratio of the extracellular matrix, impaired neovascularisation and defective macrophage function are commonly reported.[16] In all these processes, the MMP family seems to be involved.

MMP family

The MMP family consists of more than 20 structurally related, zinc-dependent endopeptidases. On the basis of the substrate specificity and domain organisation they can be divided into seven groups—collagenases, gelatinases, stromelysins, metalloelastases, matrilysins, membrane-type MMPs (MT-MMPs) and other MMPs. Family members have similar structures, with three basic domains, an amino-terminal propeptide, a catalytic domain and a hemopexin-like C-terminal domain that recognises the substrate (except MMP-7, MMP-23, MMP-26). The MMPs implicated in the wound healing process are listed in Table 1.

Discovered for their role in the degradation of extracellular proteins, MMPs are now known to ensure various functions, including the release, activation and modification of cell-signalling molecules and growth factors.[19] MMP are also involved in several physiological processes, such as leukocytes influx, angiogenesis, re-epithelialisation, and of course in the extracellular matrix remodelling that accompanies wound healing.[16]

Due to their key role in so many physiological and pathological processes, MMP activities need to be tightly regulated. This is executed at levels of mRNA transcription and stability control, at the protein level via their activators and inhibitors, including tissue inhibitors of metalloproteinase (TIMPs) or alpha-2-macroglobulin,[20] and through cellular compartmentalisation.[21,22] In the wound environment, the number and type of cells that migrate into the wound region contribute to an important part of the mechanisms of healing.

In physiological wound healing, the sequential and overlapping processes of haemostasis/inflammation, granulation, epidermisation and tissue remodelling require the production, activation and precise regulation of specific MMPs at distinct locations for precise periods of time. In chronic wounds, this delicate balance has become dysregulated and the healing process stalls in the inflammatory phase, which induces an intensified protease response.

Objectives of this review

The purpose of this review is to discuss the implications of local protease levels during the healing process of cutaneous chronic wounds, based on an analysis update of published clinical trials on this topic. More specifically, it was planned to answer the following questions:

- Do chronic wounds have higher levels of MMPs than acute wounds?
- Are the higher MMP levels observed in chronic wounds correlated with delayed wound healing?
- How could MMP-related indicators be used to

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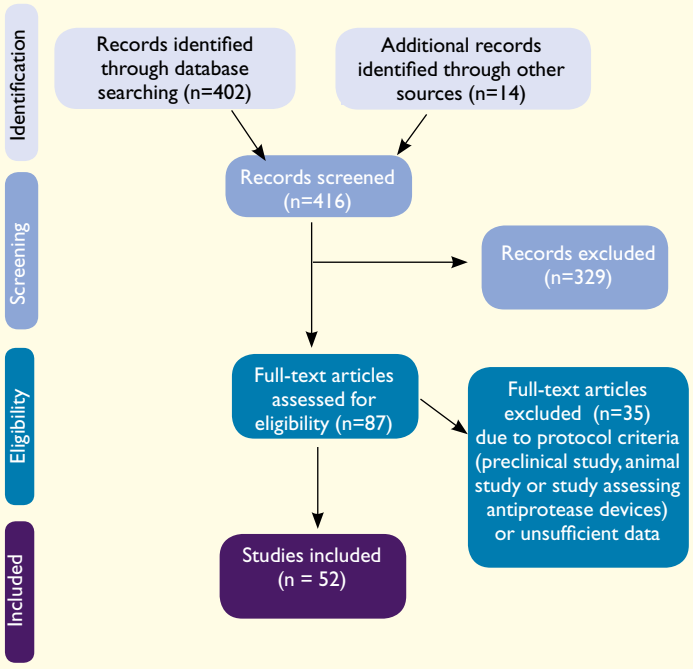
Fig 1. Flow of studies through the review



n–number of studies.

assess wound healing prognosis?
- Is there such a thing as a MMP threshold?
- Considered individually, do all chronic wounds have an elevated level of MMPs? In what proportion of patients is this the case?

In this review, neither preclinical data nor clinical trials assessing antiprotease devices or drugs will be discussed.

Methods

Literature search

The databases Medline and Embase were searched to identify clinical trials pertaining to the assessment of MMPs in chronic wounds. The searches were run in late September 2014 with the following keywords: 'metalloproteinase' or 'metalloprotease' and 'wound healing'. Clinical trials were considered for inclusion if they enrolled patients with cutaneous chronic wounds and were published in English. *In vitro,* animal or preclinical studies were excluded, as were trials on non-cutaneous wounds. In addition, references of narrative and systematic reviews were scrutinised for additional articles.

Results

Using the above strategy, the research initially returned 402 papers and, at the end of the screening process, 52 articles were selected and their clinical data analysed (Fig 1).

Review question 1: Do chronic wounds present higher MMP levels than acute wounds?

Yes, chronic wounds present higher levels of protease activity than acute wounds. This has been demonstrated through comparative trials analysing MMP levels in various populations (see Table 2 for main outcomes, classified by wound aetiology and wound sample type). Chronic wounds, including VLUs,[23–28] DFUs,[29,30] PUs,[31,32,25] dehiscent surgical wounds[32] and acute wounds that have become chronic[33], were found to have elevated MMP activity. Their MMP levels were higher than those recorded at any time in normally healing acute wounds for example, surgical wounds, including mastectomies, ablations and graft donor sites.[25,27]

This increased level of activity may be due to a combination of increased expression of MMPs, gelatinases MMP-2 and MMP-9,[23,24,27–31,34] collagenases MMP-1, MMP-8 and MMP-13,[25,29–32,34–39] stromelysin MMP-3,[37] matrilysin-2 (MMP-26)[39] and a possible down-regulation of their inhibitors TIMP-1,[24,25,31,37] and TIMP-2.[29] Among those with elevated MMPs, MMP-9 and MMP-8 usually presented in the highest concentrations, while MMP-1 presented the largest increase.[25,40]

Based on those clinical data, the trial's authors suggested that the increased proteolytic environment in chronic wounds may impede healing.[23–25,29,31,32] However, many of the first publications on the topic had limitations. For example, the analyses of chronic wounds were carried out as snapshot studies, and when examined over time the time courses were mainly unspecified. Another limitation was the relatively small size of heterogeneous population analysed in some trials. These limitations may partly explain some of the contradictory data reported as well as the heterogeneity of results observed at an individual level.[28,34,36,41–43]

Review question 2: Are the higher MMP levels observed in chronic wounds really correlated with delayed wound healing?

Before answering this question, it is crucial to define what delayed wound healing is. As there is no official definition of or consensus on an optimal wound healing rate when referring to chronic wounds, the different classifications used in the clinical trials analysed in this review have been reported in Table 3.

Using these classifications of wound healing rates, the higher MMP levels observed in chronic wounds were genuinely correlated with delayed wound healing. In addition, levels of certain MMPs seem to negatively correlate with the clinical progress of wound healing.[41,44,45] This has been demonstrated through recent comparative trials assessing both the wound healing course and levels of MMPs in various well-defined cohorts of patients with specific chronic wounds, while standards of care have been

Table 2. Characterisation of matrix metalloproteinases (MMP) and tissue inhibitors of matrix metalloproteinases (TIMP) expression in chronic wounds compared with acute wounds

Type of chronic wounds samples	Methods	Main MMP and TIMP outcomes in chronic wounds versus acute wounds	Reference
CW of various origins Biopsies	ISH	↑ MMP-1 in CW (greater number and variety of cells) ↑ MMP-3 in CW (greater number of cells) TIMP-1 detected only in AW MMP-7 not expressed	37
	IHC	↑ MMP-8 in all of the CW (weak or absent in AW) ↑ MMP-26 in AW on D1 then disappeared. In CW, present in all samples except the most prolonged.	39
CW of various origins Wound fluid	ELISA	↑ Collagenase activity in CW (not detectable in AW) ↑ IL1□ in CW	32
	ELISA	↑ Polymorphonuclear elastase, ↑MMP-2, ↑MMP-13 ↑ IL-1□/IL-6/IL-8	34
	Azocoll, ELISA Zymography	↑ Gelatinase activity (x30)—Mainly MMP-9 ↑ EGF degradation	41
	ELISA	↑ MMP-1 and MMP-8 in CW ↓ TIMP-1 in CW MMP-8 > MMP-1 in CW & AW (x100) MMP-8 in drains < open wounds Activated MMP-8 in CW / pro in AW MMP-1 activity weak in CW, undetectable in AW	25
CW of various origins Biopsies and wound fluids	ISH, IHC, ELISA	No statistical significant differences in MMP-9 and MMP-2 in wound margin tissue of CW and 7-day old AW	64
	Zymography	Different localization of MMP-9 between CW and AW	
VLU Biopsies	ISH, IHC	↑ MMP-13 (not detected in AW)	38
	ICH, WB	↑ Elastase in CW	61
	ESA	↑ Elastase in elderly	
	QRT-PCR	↑ MMP-1 mRNA in class 4 and 6	57
	WB, ICH	↑ TIMP-1 mRNA in class 6	
	Zymography	No difference in total protein levels Healthy tissues have been collected on patients with CW ↑All MMP (analysing total of pro, active and TIMP-combined forms) but MMP-7 ($p<0.005$)	
	Multiplex protein analysis	MMP-9 presented the higher concentration, followed by MMP-8, then MMP2 and MMP-1 MMP-1 presented the largest increase (x451), followed by MMP-9, -13 and -8 (x80-x130), and less than 10 fold for the others ↑ TIMP-1, TIMP-2 similar in both tissues. ↓TIMP1/MMP9 ratio ($p<0.001$)	40

taken into account in line with guidelines.

In wound fluids, MMP-9 levels correlate with the severity of ulcers,[27,28,42,43] and inversely with the healing course of VLU,[44] DFU[46] and PU.[45] Therefore:

- The more elevated the MMP-9 levels at baseline, the poorer the wound healing observed after weeks of standard treatment[44–46]
- Elevated levels of MMP-9 observed in chronic wounds at admission decreased while wound healing occurred.[26,41,44,47]

According to two studies, the MMP-9:TIMP-1 ratio would better reflect the correlation between

Table 2. Characterisation of MMP and TIMP expression in chronic wounds compared with acute wounds (continued)

Type of chronic wounds samples	Methods	Main MMP and TIMP outcomes in chronic wounds versus acute wounds	Reference
VLU Wound fluids	Gelatin zymography	↑ MMP-2 and MMP-9 (x5, x10) Active and preform present	23
	Zymography	↑ Gelatinases in a number of cases (active forms almost in all CW) ↓ TIMP-1(<1/2 of the highest value in AW)	24
	Collagenase & ESA, WB, Zymography	Low Elastase or cathepsin G ↑ Total collagenolytic activity, no difference if autoactivated ↑ Gelatinase	36
	WB	↑ ProMMP-1 and complexed MMP-1 (not detected in mastectomy) MMP-1 mostly complex to □2-macroglobulin in wounds	35
	Gelatin zymography	↑ MMP-9 (x2), presence of active MMP-9 and active MMP-2 ↑ Urokinase plasminogen activator (x2)	26
	Zymography SAS ELISA, IP	↑ MMP-9 (p<0.01) = predominant protease ↑ Type I collagenase activity (p<0.01) ↑ Type IV collagenolytic activity (a priori due to MMP-9 more than MMP-1, 8 or 13 which exhibit minimum activity)	28
VLU Wound fluids, plasma samples and biopsies	ELISA WB	↑ MMP-9 and neutrophil gelatinase-Associated Lipocalin whatever the analysed samples	44
VLU Wound site specific collection—wound margin	Gelatin zymography	↑ ProMMP-9 and pro-MMP-2 (vs any time in AW and whatever the wound healing status of the CW) Apparition of activated MMP2, activated MMP9 and Human Neutrophil Elastase (absent in AW) ↑Statistical correlation between proMMP9 and increased severity of the wound healing status of the ulcer (p=0.006)	27
PU Wound fluids	Gelatin zymography ELISA	↑ Active and potential collagenolytic activity ↑ ProMMP-2 (x10)–↑ activeMMP-2 (x4)–↑ MMP-9 (x25), p<0.01 ↓ TIMP-1 vs AW but ↑collagenases complexed TIMP-1 (x7), p=0 .001	31
DFU Biopsies	ELISA & Gelatin zymography	↑ MMP-1 (x65), p<0.01; ↑ MMP-8 (x2), p<0.02 ↑ Active MMP-2 (x6), p=0.033 ; ↑ proMMP-2 (x3), p=0.042 ↑ MMP-9 (x14), p=0.027 ↓ TIMP-2 (x2), p<0.007§	29
DFU Wound fluids	Zymography, WB, LC-MS/MS	↑ MMP-1, ↑ MMP-8 and ↑ MMP-2, presence of active MMP-2 On average, no statistical ↑ of MMP-9	30

VLU–venous leg ulcer; PU–pressure ulcer ; DFU–diabetic foot ulcer ; ISH–In situ hybridization–IHC: ImmunoHistoChemistry; WB–western blot; ESA–Elastase Substrate Assay; QRT-PCR–quantitative reverse transcriptase polymerase chain reaction; SAS–substrate activity assay; ELISA: Enzyme-Linked ImmunoSorbent Assay; LC-MS/MS:–liquid chromatography with tandem mass spectrometry; AW–acute wounds; CW–chronic wounds; MMP–matrix metalloproteinase; mRNA–messager ribonucleic acid; TIMP–tissue inhibitor of metalloproteinase

high protease activity and poor healing outcomes.[45,46] Interestingly, even in wounds with a less severe prognosis, such as with a pressure ulcer scale for healing (PUSH) score ≤11,[28] or in those considered 'improving',[27] 'high healing ulcers'[44] or 'good healers',[40] MMP levels were still higher than in acute wounds.

Considering the analysis of another kind of biological sample, it has been also reported that elevated serum concentration of MMP-9 and increased MMP-9:TIMP-1 serum ratio on one hand and elevated serum concentrations of MMP-2 and MMP-3 on

the other hand can effectively predict a poor healing outcome for DFUs[48,49] and traumatic war wounds[33] respectively. In a more recent study, an elevated global protease activity (including MMP and human neutrophil elastase), detected by a diagnostic test, appeared to be tightly associated with the failure of dermal substitute grafting in DFU management.[50]

It was then logical for the authors of these studies to suggest that:

- These factors could be used prognosis indicators[26,27,45, 46,47,33,44]
- Inhibiting MMPs (or enhancing their inhibitors) could optimise the healing course of chronic wounds.[28,41,42,47,48]

Review question 3: How could MMP-related indicators be used to assess wound healing prognosis?

This issue should be treated with caution. First, we have to remember that there are different MMPs, which have different roles during the wound healing process. These are found in different cells, in different locations, at different levels, at different times and for different durations to express their functions efficiently. The expression of MMPs is affected by various finely shaded levels of regulation.

Second, chronic wounds can have different aetiologies. The cellular and biochemical mechanisms leading to MMP dysregulation vary between aetiologies,[16] and may end up with various types or intensities of protease imbalance.[41,42,51]

To demonstrate a strong correlation between MMP levels and the course of wound healing, all the published clinical trials assessed specific markers in well-defined cohorts of patients. As long as the same marker is followed in the same population, under the same conditions of analysis, it can reasonably be assumed that the interpretation of the results would be reliable. However, any generalisation or adaptation of these correlations would make the conclusions unreliable.

For example, if a high level of activated MMP-9 has been associated with poor healing in numerous publications, inversely an elevated MMP-1:TIMP-1 ratio in DFU fluids, collected from the edge of the wound with absorbent paper strips, has been correlated to good healing.[47]

In the international consensus on 'the role of proteases in wound diagnostics', published in 2011, a group of experts agreed that 'high protease activity is the best available biochemical marker for predicting poor wound healing of both acute and chronic wounds',[52] but they also specified that 'researches are still required to clarify' numerous unanswered questions about MMPs in the wound healing process.

In conclusion, indicators related to MMPs may be used to assess wound healing prognosis. However, there is not currently enough clinical evidence for a global threshold, with an acceptable specificity and sensibility, for all kind of wounds or for heterogeneous population of wounds of various aetiology.

Table 3. Wound Healing Rate classification according to the different clinical trials analysed for this review

Venous leg ulcers (VLUs)

- Rapid healers with a RWAR > 40% after 4 weeks versus delayed healers with a RWAR < 40%.[40]
- High-healing wounds with a healing rate ≥1 cm²/week, low-healing wounds with a healing rate <1 cm²/week) or non-healing wounds without signs of healing considering the wound surface area reduction at 8 weeks.[44]
- Improving, static or deteriorating evolution of the margins of the wounds between times of collection.[27]

Diabetic foot ulcers (DFUs)

- Healed versus unhealed at 12 weeks,[46] or at 20±8 months.[48]
- Good healers with a RWAR of at least 82% at 4 weeks and otherwise poor healers.[47,49]
- Integration or not of dermal graft at 4 weeks.[50]

Pressure ulcers (PUs)

- Good healers with at least a 85% RWAR over 36 days; intermediate healers with a RWAR comprise between 45 and 85% and poor healers with a RWAR of less than 45%.[45]

Traumatic war wounds (firstly categorised as acute wounds)

- Impaired or delayed wound healing or dehiscence wound: >21 days from injury or normal wound healing: <21 days.[33]

VLU–venous leg ulcer; RWAR–relative wound area reduction; DFU–diabetic foot ulcer; PU–pressure ulcer

Review question 4: Is there such a thing as a MMP threshold?

As for the previous questions, the answer to this MMP threshold question will depend on what it is related to.

Among all the studies that have demonstrated a correlation between MMP levels and the stage of wound healing, only three have proposed an MMP level cut-off, based on a receiver operating characteristic analysis.[46,47,48] To predict wound closure, these trials have analysed MMP levels only in specific cohort of patients with DFUs.[46,47,49] Analysing different biological samples (wound fluids or serum) and different subgroups of DFUs (purely or mostly neuropathic, infected or not), each of these studies has identified a 'best threshold' to predict wound healing, although all three different, as reported in Table 4.

Interestingly, the three studies proposed a threshold based on a combination of markers (e.g. MMPs + TIMPs +/- transforming growth factor-beta), rather than a strict MMP threshold. It is also noteworthy that none of the studies analysed or discussed the costs of the decisions that would be made based on their identified threshold, and that, since they were published, these thresholds have not been tried and assessed in real life yet.

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Table 4. Wound healing predictive value of MMP Levels in cohorts of patients with DFUs: specificity and sensibility of the identified thresholds

Studied Population	Biological sample, MMP detection method and outcome predicted	Best cutoff for wound healing predictive value of MMP levels at presentation	Reference
DFUs (n=62) mostly neuropathic (77%) Grade A to D (TWC)—Antibiotics for 83% of patients Mean ulcer area: 3.2 cm^2 Mean ulcer duration: 118 days Following period: 12 weeks Debridement, offloading and standard cares	Wound fluid Gelatin zymography and ELISA Wound healing at week 12	ProMMP-9 + TIMP-1 >480 pg/ml + TGF-β1 >115 pg/ml Sensitivity: 87% Specificity: 91% Area under the curve 0.94*	46
Neuropathic DFUs (n=93) Grade 1 to 3 B (TWC)—Antibiotics for 97% of patients Posterior tibial and pedal pulses or ABPI≥0.9 Ulcer area from 0.5 to 3.2 cm^2 Ulcer duration from 18 to 51 days Following period: 12 weeks Debridement, offloading and standard cares	Serum ELISA RWAR of 82% at week 4	MMP-9/TIMP-1 ratio <0.395 Sensitivity: 63.6% Specificity: 58.6% Area under the curve 0.66†	49
Neuropathic DFUs (n=16)‡ Grade 1 to 3 A (TWC) Not infected, no severe arteriopathy Posterior tibial and pedal pulses or ABPI≥0.9 Ulcer area from 0.95 to 5.1cm^2 Ulcer duration from 1 to 6 months Following period: 12 weeks Standard care/no dressing or drug known to interfere with MMP levels	Wound fluid Gelatin zymography and ELISA RWAR of 82% at week 4	MMP-1/TIMP-1 ratio >0.39 Sensitivity: 71% Specificity: 87.5% Area under the curve: 0.82	47

MMP–matrix metalloproteinase; DFU–diabetic foot ulcer; TWC–Texas Wound Classification; ABPI–ankle brachial pressure index; ELISA–enzyme-linked immunosorbent assay; RWAR–relative wound area reduction; TIMP–tissue inhibitor of metalloproteinase; TGF–transforming growth factor. ‡The 16 patients included are reported to present DFU with grade 1–3A according to the TWC, during the study, two patients have received oral antibiotics for proven osteomyelitis, and an IPS<0.9 was later detected in four patients. Due to the small number of patients included in this trial, these bacterial and ischemic contributions may have partially influence some of the results.
*p<0.00001 †p<0.001

Besides, it should be underlined that no study mentioned a global MMP threshold (for multiple MMP types in the same time) and emphasised that there is no evidence that a global MMP threshold could be universally relevant for wounds of all types of aetiologies. A relevant threshold (with high sensibility and specificity) determined in one aetiology such as DFU might be less relevant or irrelevant (with more false negatives or positives) in another aetiology. A standard threshold would be surprising

Table 5. High MMP related outcomes prevalence according to published trials

Outcomes related to an initial higher level of MMP indicators	Prevalence of the wounds with the high MMP related outcomes	Ref.
Unhealed DFUs at 12 weeks	63% (n=39/62)	46
Unhealed DFUs at 12 weeks	47% (n=14/30)	48
Poor healers (DFU) with a RWAR <82% at 4 weeks	54% (n=50/93)	49
Total (Poor + intermediate PU healers)	79% (n=44/56)	45
Poor healers (PU) with a RWAR of less than 45% over 35 days	*14% (n=8/56)*	
Intermediate healers (PU) with a RWAR comprise between 45 and 85% over 35 days	*64% (36/56)*	
Total (Non-healing + low healing VLUs)	58% (n=18/31)	44
Non-healing VLUs without signs of healing considering the wound surface area reduction at 8 weeks	*23% (n=7/31)*	
Low-healing VLUs with a healing rate <1 cm²/week considering the wound area reduction at 8 weeks	35% (n=11/31)	
Total (Deteriorating + static VLUs)	69% (n=118/171)	27
Deteriorating wounds (receding margins based on independent blind evaluation that occurred less than 8 weeks after time of sample collection)	*54% (n=92/171)*	
Static wounds (no net change of wound margins according to blindly assessment that occurred less than 8 weeks after time of sample collection)	*15% (n=26/171)*	
Bad VLU responders under compression (Healing <40% after week 4)	38% (n=11/29)	40
Impaired or delayed traumatic war wounds healing or dehiscence wound (>21 days from injury)	24% (n=9/38)	33

DFU–diabetic foot ulcer; RWAR–relative wound area reduction; PU–pressure ulcer; VLU–venous leg ulcer

given that wounds of different aetiologies usually present different levels of MMPs,[41] and even subgroups of wounds of the same aetiology (such as neuropathic and ischaemic DFUs) present statistically different levels of MMPs.[42]

In conclusion, until now, there is no consensus on the value of the best MMP threshold that could be used to predict general wound healing, not even in DFUs, although it is in this type of wound that the rare published thresholds have been determined.

Review question 5: Considered individually, do all chronic wounds have an elevated level of MMPs? In what proportion of patients is this the case?

Obviously, this will depend on the definition of an 'elevated' level, as this term is relative.

Like numerous other biological markers, MMP levels present an important inter-individual heterogeneity.[25,28,29,30,34,36,41] The same heterogeneity has also been reported when assessing other proteases such as elastase,[34] extracellular matrix or growth factor like epidermal growth factor degradations,[53,54] and, of course, important heterogeneity in wound healing rates has been observed in chronic wounds.[27,44–46,49] The heterogeneity in MMP levels could be explained at different levels:

- Different wound aetiologies,[16,41,43,51]
- Different subgroups of wounds due to specific characteristics of the patient, the wound or the treatment[28,40,55–58]
- Individual variability/genetic factors[43]
- Different studied markers (MMP species) and methods of detection[36,59]
- Different phases of the wound healing process.[26,27,34,45]

For this reason, heterogeneous studied groups represent a tricky issue as it cannot be confidently determined how their median MMP levels should be

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considered, compared to those of finely defined groups of wounds. Regardless of this, it is ultimately important to remember that 'high' and 'low' MMP qualifiers are always determined in regards to a specific outcome in a specific cohort of patients. Table 5 presents high-MMP related outcomes and their prevalence according to the trials analysed in this review.

The first trials assessing the MMP issues have reported that chronic wounds have higher MMP levels than acute wounds, with an important heterogeneity reported at the individual level, partially because non-homogenous groups were studied. More recent trials have demonstrated that even within the 'chronic' wound group, differences can be observed; the MMP profile changes during the chronic wound healing course and some subgroups of wound/patient with a poorer wound healing prognosis/course have higher levels of MMPs than others. However, clinical trials that have compared 'well-healing chronic wounds' with acute wounds have confirmed that chronic wounds always exhibit, on average, higher levels than acute wounds.[27,28,40,44] Furthermore, some studies have suggested that elevated levels of certain MMPs might even be present before the appearance of chronic wounds; if this postulate is true, this might imply that chronic wounds will always have higher levels of MMPs, at least at the beginning, when the wound occurs and settles into its inflammatory phase.[48,57,60]

According to the published clinical evidence, some subgroups of patients have higher levels of MMPs: those with ischaemic DFUs,[42] people with PUs with a PUSH score ≥12,[28] poor VLU responders under compression,[40] patients with hypertension[55] and elderly patients.[58,61] And, as healed ulcers still present higher MMP levels than acute wounds, it could be hypothesised that recurrent VLUs may also exhibit high levels of MMPs.[57] All these patients should be seriously considered as a priority for possible treatment of their MMP issue.

The proportion of chronic wounds with high levels of MMP activity could, however, be evaluated at:

- ~40–60%, considering the wounds that actually do not heal after 12 weeks of treatment and for which a high level of MMPs has been reported[46,48,49]
- ~60–80%, considering wounds categorised as non-healing and as poor or intermediate healing and for which a high level of MMPs has been reported[27,44,45]
- Almost 100%, considering that higher levels of MMPs have been reported in chronic wounds compared with acute wounds and assuming that their healing course can still be optimised even for what are today considered as 'good healers'.[27,28,40,44]

Additionally, around 30% of certain specific wounds, such as traumatic war injuries or wounds suitable for grafting, can also exhibit high levels of MMPs.[33]

This does not mean that proteases are the only ones to blame for non healing, but that treating MMP issues might help reset wounds and put them back on the right healing trajectory, in combination—of course—with aetiological treatments and good standards of care (including compression therapy in VLUs, off-loading in DFUs and mechanical or sharp debridement).

Conclusion

Chronic wounds are characterised by a protease imbalance that delays their healing process.

In this clinical evidence review, initial high levels of MMPs have been correlated to significant delayed wound healing in chronic wounds of various aetiologies (DFUs, VLUs, PUs and dehiscent surgical wounds) or even in acute wounds that have become chronic. These elevated levels tend to decrease while the wounds are put back on their right healing trajectory and wound healing occurs. Therefore, it would be of interest that more research further assesses the efficacy of anti-protease treatment in these wounds.

Is it still possible to improve the healing course of these wounds? Have their optimal healing rate really been already reached? Could the possible improvement imply a protease modulating dressing? Would it be effective? The answer to these questions will also depend on the efficiency of the applied wound dressing.

At the end of the day, once high MMP levels have been detected in a wound, practitioners will still have to choose the best protease-modulating treatment based on best evidence. To date, numerous devices or compounds have been claimed to have an effect on MMP levels but, to our knowledge, there is no recognised exhaustive or agreed list of these MMP-related treatments.

In a recent review on dressings improving venous leg ulcer healing, Raffetto pointed out that 'therapies directed at modulating MMPs may have promise in ulcer healing',[62] and highlighted the results of four randomised controlled trials (RCTs) assessing two recognised modulating MMPs devices: nano-oligosaccharide factor (TLC-NOSF matrix) dressings; and oxidized regenerated cellulose/collagen (ORC/collagen matrix) dressings. These RCTs compared these two devices with standard dressings[63,64,65] and with each other[66], and found them to have encouraging and significant results on the wound area reduction and healing rate.[65,66]

A large, systematic review of the preclinical and clinical evidence on protease-modulating treatments would better document the evidence on these devices and provide a more accurate overview of the solutions that could help to achieve the optimal healing rates in chronic wounds. ■

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