Using a protease test to inform wound care treatment decisions

KEY WORDS
- Wound care
- Assessment
- Protease test
- Cost-effective

Across the NHS, clinicians are being asked to deliver the same level of care, or improved care, with the same level of resources. One way to do this is to begin using innovative technologies, which can save resources in terms of staff time and improved decision making. This article examines how a new protease test, which allows practitioners to measure elevated protease activity within the wound bed, can potentially result in better-informed cost decisions, avoidance of unnecessary interventions, shorter overall treatment duration and earlier recognition and prevention of wound complications.

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The field of tissue viability is not alone in finding that the current financial pressures are having an impact on service delivery. Resources are becoming scarce and there is the inevitable drive to provide a high standard of care with an ever-diminishing budget. This heralds the way for reflection on current practice and an opportunity of finding new and innovative ways of working that will enable clinicians to deliver a high standard of wound care within the fiscal constraints.

The latest consultation document from the Chief Nursing Officer — *Developing the Culture of Compassionate Care* — proposes a new vision for nursing, midwifery and care provision. It sets out the values of compassionate care and asks how they can be developed further across health and social care (Department of Health [DH], 2012). Integral to the proposal is the delivery of high-quality care and measuring impact, specifically using technology to:

- Support productivity and efficiency
- Promote safe practice
- Enable care to be provided in new ways
- Support decision making.

THE IMPORTANCE OF PROTEINASE IDENTIFICATION

There are four recognised components to the wound healing process:

- Inflammation
- Destruction
- Proliferation
- Maturation.

Protease activity is a normal recognised part of this process. The proteases assist in the removal of damaged tissue especially the extracellular matrix (ECM), the scaffold into which new blood vessels grow and upon which granulation tissue is formed. Proteases also cleave pathways within the wound bed for cells to move along. Proteases are in an inactive form and are turned on by other proteases when they are required to function. Once activated, they are able to bind to, and attack, their target — often referred to as a substrate (Gibson et al, 2009).

Proteases are produced by either activated inflammatory, cells such as neutrophils and macrophages, or cells involved in the healing process, such as epithelial cells, fibroblasts and vascular endothelial cells — these are referred to as endogenous proteases (Gibson

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et al, 2009). Endogenous proteases are produced by the body, whereas exogenous proteases form via external sources, such as bacteria. Examples of endogenous proteases include collagenase, gelatinase and elastase, whereas exogenous proteases are produced by bacteria found in the wound bed (Walker et al, 2007).

As well as producing proteases, the activated inflammatory cells also generate cytokines, which are part of the cell-to-cell communication system and help to regulate protease activity — the cytokines themselves manufacture additional proteases (Tarnuzzer and Schultz, 1996). As the proteases assist in the removal of damaged tissue, controlled degradation by the proteases is necessary for normal wound repair (Cullen et al, 2002).

The fact that the proteases degrade the ECM is reflected in their name — matrix metalloprotease (MMPs) — the 'metallo' reflecting the need for an ion component within the protease to allow them to function.

During their activity, proteases induce a biological reaction within the wound bed, but themselves remain (Gibson et al, 2009). Following wounding, the protease levels peak at day three and reduce at day five (Nwomeh et al, 1998). This reflects the stages of the wound-healing process with the initial inflammatory stage lasting from 1–3 days and resolving by day five.

Therefore, normal wound healing is a carefully controlled balance of destructive processes, necessary to remove damaged tissue, and repair processes that lead to new tissue formation (Cullen et al, 2002).

Growth factors play a pivotal role in this balance by stimulating cell proliferation and the subsequent repair process. However, growth factors are an additional target for proteases, which can render the growth factor impotent and halt the repair process. The balance between protease activity and inactivity is achieved by the introduction of tissue inhibitor MMPs (TIMPs), which dampen down the activity of proteases once the required amount of damaged tissue has been removed. The TIMPS down-regulate the protease activity, thus preventing any further action by the proteases, which could result in degradation of the newly formed granulation tissue and prevention of migration and attachment of cells (Greener et al, 2005). Tissue may be attacked by several MMPs — the main ones identified in wound healing are MMPs 1, 2, 8 and 9 (Gibson et al, 2009).

However, if growth factors and extracellular matrix proteins are to be protected from degradation then it is necessary to control the activity of proteases, and in particular human neutrophil elastase, which has been shown to be the predominant protease causing this proteolytic damage (Yager et al, 2007).

The proteolytic activity and subsequent degradation of growth factors contribute to the net tissue loss associated with chronic wounds. It has been established that in non-healing wounds there are elevated levels of proteases and a lack of fibronectin, which is normally present in the ECM and is an important element in communication between growth factors (Herrick et al, 1992). In this situation, the levels of proteases remain high due to by-products of the inflammatory process, such as the production of oxygen-free radicals (Trengrove et al, 1999).

In addition, bacteria in the wound bed produce exogenous proteases and, therefore, indirectly stimulate the inflammatory response (International Consensus, 2011). Consequently, in a non-healing wound proteases shift the balance from synthesis to degradation — they degrade growth factors and the newly formed extracellular matrix (International Consensus, 2011).

DETECTION OF ELEVATED PROTEASE ACTIVITY IN THE WOUND BED

Elevated protease activity is a biochemical marker for predicting poor wound healing in acute and chronic wounds. Therefore, it is important that elevated protease levels are detected as soon as possible to prevent a wound ending up in a static state of permanent inflammation.

However, there are no clinically visible signs that can specifically identify elevated protease levels in a wound bed. Although clinicians may be able to

recognise inflammation by the cardinal signs of pain, redness, heat and swelling, they cannot visually distinguish between normal inflammation, seen at the initial stage of wounding, and inflammation caused by abnormally elevated protease levels.

If they were able to detect abnormally elevated levels of protease activity, clinicians would be able to detect barriers to healing and implement timely corrective action (International Consensus, 2011).

NEW TECHNOLOGY

A recent development in tissue viability may offer a way forward when attempting to detect abnormally elevated levels of protease activity. WoundChek™ Protease Status (Systagenix), is a point-of-care test that allows practitioners to measure elevated protease activity in the wound bed.

As mentioned above, hard-to-heal wounds often have elevated protease activity, which, if identified, can assist clinicians in the wound assessment process and subsequently guide the choice between various treatment options.

This is a pragmatic example of a new way of working in the tissue viability arena. However, any test should only be performed if it is possible to react to the result, and the subsequent care should have a positive effect on patient outcome (World Union of Wound Healing Societies [WUWHS], 2008).

The WoundChek Protease Status has provided clinicians with a test method that can identify elevated protease levels in a wound bed.

PROTEASE MODULATION

Once detected, reduction of elevated protease activity in the wound should become a clinical priority and may be achieved by several methods.

Indirect methods include removing the protease-rich wound fluid, thus reducing the protease activity.

A reduction of the wound bioburden and debridement of biofilms, will also indirectly impact on the production of exogenous proteases. Another therapeutic option is using compounds that scavenge reactive oxygen species/free radicals — by perpetuating the inflammatory response they keep the wound in a state of chronic inflammation and prevent it moving through the healing trajectory.

Direct or active modulation includes interfering with MMP gene expression, which will affect the major control mechanism for MMP synthesis and activity, along with binding and inactivating and or neutralising the MMPs (Eming et al, 2008).

Protease action and activity is pH–dependant and non-healing wounds generally have a pH level of 8. If the pH level is reduced to a more acidic level (approximately 4) the protease activity is reduced by approximately 80% (Greener et al, 2005).

These actions now offer a supplementary component to the already established principles of wound management — treat the underlying cause and optimise the wound bed and patient condition (International Consensus, 2011) — and include modulating the protease activity through the use of a category of protease-modulating dressings.

These dressings have the potential to confuse clinicians as they do not all work in the same way to modulate proteases and clarification is needed to enable the clinician to choose the optimal method for the patient.

In order to compile the list below, the author contacted manufacturers with a dressing in the protease-modulating category and requested information on their products' mode of action and evidence to support these claims (Cutisorb Ultra® [BSN Medical] and ActivHeal AquaFiber [Advanced Medical Solutions] do not promote these dressings primarily for protease modulation, therefore, they are not discussed further in this article).

It is also suggested that honey and negative pressure wound therapy (NPWT) have a role in protease modulation, however, they are not always listed as protease-modulating dressings (Stephen-Haynes and Callaghan 2011, Moues, 2008).

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Table 1
Protease-modulating action

Protease modulating dressing	*DIRECT*			*INDIRECT*					
	Binds and inactivates and/or neutralises MMPs	*Binds and inactivates and/or neutralises elastase*	*Alteration in protease gene expression*	*Reduction in wound bioburden*	*Debridement*	*Scavenging and or binding of reactive oxygen species/free radicals/cytokines*	*Reduction in wound bed pH*	*Removal of proteases from the wound bed*	*Binds and protects growth factors*
Aquacel, Aquacel Extra	×					×			
Auacel AG	×			×		×			
Cadesorb							×		
Curea P1 & P2	×			×				×	
Dry Max Extra	×								
Durafibre								×	
Flaminal Forte Flaminal Hydro				×					
Flivasorb						×			
Iodozyme Oxyzyme				×			×		
Promogran	×	×				×	×	×	×
Promogran Prisma	×	×		×		×	×	×	×
Sorbion Sachet Extra Sorbion Drainage Sorbion Sana				×	×				
Suprasorb C						×			
Tegaderm Matrix			×			×			
UrgoStart, UrgoStart Contact UrgoClean	×							×	

DRESSINGS/PRODUCTS

Aquacel®, Aquacel® AG, Aquacel® Extra™ (ConvaTec)

What is it?

The various Aquacel dressings comprises a soft, sterile, non-woven pad or ribbon dressing composed of Hydrofiber® (ConvaTec) (sodium carboxymethylcellulose).

How does it modulate protease activity?

The dressing absorbs oxygen free radicals and the fibrin layer that is produced between the dressing and the wound bed acts as a physical barrier preventing them returning into the wound bed (Hoekstra et al, 2002). The dressing binds and immobilises MMPs (Walker et al, 2009; Walker and Parsons, 2010) and the

antimicrobial activity of the silver kills bacteria (Newman et al, 2006).

Cadesorb® (Smith & Nephew)

What is it?

White starch-based sterile ointment.

How does it modulate protease activity?

It reduces local wound pH to 5 (Greener et al, 2005).

Curea P1 and Curea P2 (Bullen Healthcare)

What is it?

A fluid-permeable polypropylene wound contact layer with a fluid-impermeable vapour-transmitting back-sheet. Also has an absorbent core, which contains a gelling agent.

How does it modulate protease activity?

Proteases and bacteria are absorbed and then bound into the dressing (Bullen Healthcare, data on file 2011).

DryMax® Extra (Absorbest)

What is it?

Superabsorbent polymers contained within a polypropylene sachet.

How does it modulate protease activity?

It binds and immobilises MMPs and bacteria by absorbing the exudate that contains the proteases.

Durafiber® (Smith and Nephew)

What is it?

A strong, gelling, fibre dressing.

How does it modulate protease activity?

Absorbs proteases into the dressing.

Flaminal® Forte/Hydro (Flaminal)

What is it?

Alginate gel containing two antimicrobial enzymes; glucose oxidase and lactoperoxidase (Hydro contains a lower proportion of the alginate component).

How does it modulate protease activity?

It has an antimicrobial activity that lowers the wound bioburden and thus the production by bacteria of exogenous proteases (White, 2006; DeSmet, 2009).

Flivasorb® (Activa Healthcare)

What is it?

Superabsorbent, low sensitivity wound dressing with non-adherent, white, wound contact layer and blue, outer clothing-protection layer, which contains a sodium polyacrylate superabsorber particles and cellulose.

How does it modulate protease activity?

The polyacrylate superabsorber inhibits the formation of free radicals *in vitro* (Wiegand et al, 2009a; Wiegand et al, 2009b).

Iodozyme® and Oxyzyme® (Archimed)

What is it?

Hydrogel sheet dressing with an active enzyme system, which produces iodine. Oxyzyme produces a lower level of iodine.

How does it modulate protease activity?

The mechanism of protease modulation is by reduction of pH through production of gluconic acid (by the glucose oxidase enzyme in the enzyme gel) and the antimicrobial activity of the iodine.

Promogran (Systagenix)

What is it?

An oxidised regenerated cellulose and collagen (ORC/collagen) dressing.

How does it modulate protease activity?

It binds and inactivates proteases (in particular MMP 2 and 9 in addition to elastase) and absorbs oxygen free radicals and excess metal ions. It simultaneously binds and protects growth factors (specifically platelet-derived growth factor [PDGF], epidermal growth factor [EGF] and vascular endothelial growth factor [VEGF]) and delivers them back into the wound bed in a biologically active form (Veves et al, 2002; Nisi et al, 2005; Vin et al, 2002; Wollina et al, 2005; Lazaro-Martinez et al, 2007, Synder et al, 2010).

Promogran Prisma® (Systagenix)

What is it?

The same composition as Promogran with the addition of ORC-silver, which makes the dressing maxtrix denser.

How does it modulate protease activity?

It offers the same protease inactivation as Promogran but the silver is released gradually as the ORC matrix biodegrades (relative to the level of wound exudate). This provides an antibacterial action against common wound pathogens and reduces the level of bacterial-induced cytokines (Synder et al, 2010; Braumann et al, 2011).

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Sorbion Sachet Extra, Sorbion Drainage, Sorbion Sana (h&r Healthcare)

What is it?

A hypoallergenic polypropylene outer sheath containing mechanically modified cellulose fibres with superabsorbent polymer gelling agents. Sorbion Sana is an atraumatic version.

How does they modulate protease activity?

They bind and immobilise microorganisms (Westgate and Cutting, 2012; Wiegand et al, 2012a) as well as debriding non-viable tissue (Romanelli et al, 2012).

Suprasorb C (Activa Healthcare)

What is it?

Pure, open-pore, bovine, collagen dressing.

How does it modulate protease activity?

The collagen in the dressing binds cytokines (Wiegand et al, 2012a)

Tegaderm™ Matrix

What is it?

Polyhydrated ionogen-impregnated dressing is composed of a mixture of metal ions in a citric acid-buffered ointment.

How does it modulate protease activity?

It reduces reactive oxygen species (Van den Berg et al, 2003). It effects gene expression and, therefore, the synthesis of MMPs (Monroe et al, 2005).

UrgoStart, UrgoStart Contact, UrgoClean (Urgo Medical)

What is it?

UrgoStart is a foam dressing, whereas UrgoStart Contact is a non-occlusive contact layer and UrgoClean is an absorbent dressing. These dressings incorporate lipido-colloid technology (TLC), which allows them to combine lipido-colloid particles in a non-occlusive fine mesh or within a foam dressing.

How does it modulate protease activity?

All of these dressings bind and neutralise MMPs to remove them from the wound bed (Bernard et al, 2008; Meaume, 2011).

DISCUSSION

As far back as 1996, the identification of active proteases in wound fluids was said to be essential in developing strategies to reduce their elevated levels in non-healing wounds. Therapies that establish an environment in non-healing wounds that permits growth factors and proteases to function normally should lead to healing (Tarnuzzer and Schultz, 1996).

WoundChek Protease Status is a is a test that allows clinicians to detect elevated protease activity in wound fluid. Identification of elevated protease activity can potentially result in informed cost-effective decisions, avoidance of unnecessary interventions, shorter overall treatment duration, and earlier recognition and prevention of wound complications (International Consensus, 2011).

The aim of the test is to ensure treatment is targeted specifically at the patients who will benefit most from them. It should be used as part of an integrated and structured approach to wound assessment and management (WUWHS, 2008).

Once elevated protease activity has been identified, a protease-modulating product can be used to lower the amount of proteases in the wound bed and consequently move the non-healing wound into a healing trajectory.

However, not all protease-modulating dressings have the same mode of action and the clinician should be aware of the differences before choosing a product.

Retesting the wound bed after using a protease-modulating dressing will help to evaluate the effectiveness of the product's specific protease-modulating mode of action. As with other wound care interventions, using a protease-modulating product for a limited time period prevents extended use (Best Practice Statement, 2011).

Generally, protease-modulating dressings can be found under the specialist category in wound care formularies. However, due to the significant numbers of non-healing wounds in the community setting, an alteration in attitude and practice is required, which will help generalist practitioners to take on the assessment and management of elevated proteases in non-healing wounds. WUK