Using a protease test to inform wound care treatment decisions

Trudie Young

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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.

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.

The importance of protease 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 clear 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).

The 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...
Normal wound healing is a complex process involving the coordinated actions of cells, growth factors, and extracellular matrix degradation. The balance between protease activity and inactivity is achieved by several mechanisms. The TIMPs (tissue inhibitors of metalloproteinases) down-regulate the activity of proteases once the required protease activity and inactivity is achieved (Herrick et al, 1992). In this situation, the levels of proteases remain high due to by-products of the inflammatory response, although they are prevented from producing free radicals (Trengove et al, 1999).

Therefore, in bacteria in the wound bed produce endogenous 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 as they degrade growth factors and increase 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 wound breakdown and achieve 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 recognize 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 (Syngenta), 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 are often caused by 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. A point of care 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 reducing the protease-rich wound fluid, thus reducing the protease activity.

A reduction of the wound bioburden and elimination 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 perpetrating 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 or neutralising the MMPs (Emm et al, 2008).

Protease activity 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 — treatment of the wound bed and patient condition (International Consensus, 2011) — and include modulation of 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 (Cutsor Ultra® [BSN Medical] and ActivHeal Aquafiber® [Advanced Medical Solutions]) do not promote the 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 anti-protease dressings (Stephen Haynes and Callaghan 2011, Mousse 2008).
Table 1

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<tr>
<th>Protease-modulating dressing</th>
<th>DIRECT</th>
<th>INDIRECT</th>
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<tr>
<td></td>
<td>Bed and inactivates and/or neutralises MMPs</td>
<td>Bed and inactivates and/or neutralises elastase</td>
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<td></td>
<td>Alteration in protease gene expression</td>
<td>Reduction in wound biomass</td>
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<td>Scouring and or binding of reactive oxygen species/free radicals/cytokines</td>
<td>Reduction in wound bed pH</td>
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<td>Aquacel, Aquacel Extra</td>
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<td>Cadesorb</td>
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<td>Curase P1 &amp; P2</td>
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<td>Tegaderm Matrix</td>
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<td>UrgoStart, UrgoStart Contact UrgoClean</td>
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References

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 inactivates 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? A strong, gelling, fibre dressing.

How does it modulate protease activity? It 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 (Vesav et al. 2002; Nesi et al. 2005; Yin et al. 2002; Woolina et al. 2005; Lazarou-Martinez et al. 2007; Synder et al. 2010).

Promogran Prisma® (Systagenix) What is it? An oxidised regenerated cellulose and collagen (ORC/collagen) dressing.

How does it modulate protease activity? It binds and inactive 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. (Van Torn et al. 2005; Van Torn et al. 2005; Lazarou-Martinez et al. 2007; Synder et al. 2010).
Sobion Sachet Extra, Sobion Drainage, Sobion Sana (h&r Healthcare)

What is it?
A hypoallergenic polypropylene outer sheath containing mechanically modified cellulose fibres with superabsorbent polymer gelling agents. Sobion Sana is anatraumatic version.

How does it 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 permit 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 modes 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.