Protease Activity Levels Associated with Healing Status of Chronic Wounds

T Serena1, B Cullen2, S Bayliff3, M Gibson4, D DeMarco3, J Galbraith4, N Le5, M Mancinelli5, M Sabo5, J Samies6

1Serena Group, Warren, PA, USA. 2Systagenix, Gatwick, UK. 3St. Vincent’s Health Center, Erie PA, USA. 4Miami Valley Hospital, Dayton OH, USA. 5Snyder Institute for Vascular Health and Research, Kittanning, PA, USA. 6Orangeburg Regional Medical Center, Orangeburg, SC, USA.

BACKGROUND

It is widely accepted that an elevated level of protease activity (EPA) in chronic wounds impedes healing. However, there has been little progress in quantifying an actual level of protease activity that is detrimental to wound healing. The aim of this study was to determine the relationship between inflammatory protease activities and wound healing status. Through clinical studies we have established the level of inflammatory protease activity (EPA) above which matrix metalloproteinases ( MMPs) and elastase activities correlate with non-healing chronic wounds. This is the first time that a level of protease activity has been published which shows that above which the wound status is considered to be non-healing.

OBJECTIVES

• To define elevated protease activity (EPA) associated with non healing chronic wounds
• To show the correlation between EPA and healing status of chronic wounds.
• To establish an optimal sample collection technique for prospective tests for EPA

METHODS

The study was carried out across 4 wound healing centres in the USA. Wound swabs were taken from chronic wounds including diabetic foot ulcers, pressure ulcers and venous leg ulcers. The swabs were frozen and sent to an in-house laboratory for measurement of inflammatory protease activity. Human neutrophil elastase and MMP activity was measured using fluorogenic substrates, using a “for research only” method. The healing trajectory of the wounds was retrospectively calculated according to the percentage reduction in wound area over the previous 2 - 4 weeks. Wounds were defined as healing if the wound area reduced by at least 50% for diabetic foot ulcers or 30% for both pressure ulcers and venous leg ulcers over 2 - 4 weeks. Any wounds not meeting this percentage reduction in wound area were classed as non-healing.

RESULTS:

28% of non-healing chronic wounds had EPA. This demonstrates that not all non-healing wounds are due to elevated protease activity as there were a number of non-healing wounds with low protease activity. This supports the hypothesis that there are a range of other factors that could also lead to delayed wound healing.

CONCLUSIONS

• A chronic wound with EPA, as defined by this research, has a 90% probability it won't heal*
• 28% of non-healing chronic wounds have EPA
• A test that identifies which wounds have EPA would identify wounds that are non healing due to elevated protease activity , which could lead to targeted treatment with protease modulating therapies, to increase the chance of healing in these wounds.
• Wounds with low protease activity may be non-healing for other reasons

DISCUSSION

Interestingly we also noted that, wounds with high levels of elastase activity did not necessarily have high levels of MMP activity and vice versa. This shows that an individual protease is not causative of the excessive protease activity (EPA) found in a wound and that a wound does not need to have high levels of all proteases to be non-healing. Instead individual proteases seem to be able to compensate for one another in providing a highly proteolytic wound environment. This highlights the need to measure multiple proteases in order to determine if proteolytic activity is causing a problem in the wound and preventing it from healing.

Inflammatory protease activity, namely MMP and elastase activity, is indicative of non-healing wounds when assessed to be above the levels identified in this study, and those are clinically relevant. The use of a diagnostic test able to assess protease activity in clinical practice could enable clinicians to identify wounds that are non-healing due to elevated protease activity (EPA). This could in turn aid treatment decisions and enable the targeted use of protease modulating dressings.

* These references demonstrate that the percentage reduction in wound area over 4 weeks is a good prognostic indicator of healing status.