COMMENTS AND RESPONSES

Increased Matrix Metalloproteinase-9 Predicts Poor Wound Healing in Diabetic Foot Ulcers

Response to Liu et al.

In a recent study by Liu et al. (1), the complex mechanisms of diabetic foot ulcers were further elucidated. In a series of 62 ulcers, the authors report that they found—for the first time—a positive correlation between a high matrix metalloproteinase-9 (MMP-9)–to–tissue inhibitor of metalloproteinase-1 (TIMP-1) ratio and poor wound healing.

However, these are not the first data enhancing the putative role of MMP-9 in the pathogenesis of chronic wounds. Ladwig et al. (2) also described a positive correlation between a high MMP-9–to–TIMP-1 ratio and poor wound healing in 56 patients with pressure ulcers. In 2006, Lobmann et al. (3) observed that the MMP-9–to–TIMP-2 ratio was significantly reduced in a group of diabetic patients treated with a protease modulating matrix, their healing rate being more rapid than in a group of patients receiving "good standard wound care."

Last year, in a homogenous group of 16 patients with neuropathic diabetic foot ulcers (excluding ischemic ulcers, a possible confounding factor), we found that activated MMP-9 tends to be higher in poorly healing diabetic foot ulcers (4).

As previously stated by Lobmann et al. (5), healing of diabetic foot ulcers may be delayed because of an exaggeration of their inflammatory phase, leading to increased levels of proteases and decreased levels of growth factors. In such cases, MMP-9 secreted by inflammatory cells should logically be a potent predictive factor for poor healing.

In contrast, our study also points out for the first time a positive correlation between a high MMP-1/TIMP-1 ratio and good healing ($r = 0.65$, $P = 0.008$) (4), suggesting that the MMP-1/TIMP-1 ratio could be a predictor of good wound healing in diabetic foot ulcers. We consider it biologically relevant that a high level of MMP-1 is associated with favorable wound healing because MMP-1 is indispensable for migration of keratinocytes and thus for re-epidermization. Furthermore, it has been suggested that an adapted regulation of MMP-1 is essential to the proper progression of the healing process (5).

Lastly, as we monitored the MMP levels throughout a longitudinal 12-week study, we can also suggest that the pattern of MMP levels is different between "good healers" and "bad healers," with an earlier decrease in levels of MMP-8 and MMP-9 secreted by inflammatory cells.

In conclusion, pathophysiology of diabetic foot ulcers is complex and not completely elucidated. MMPs are key proteases implicated in wound healing. A better knowledge of their pattern of expression, especially in chronic wounds, should allow for a better evaluation of the prognosis of diabetic foot ulcers, as well as new dressings targeted at inhibiting some of these MMPs.

MARIE MULLER, MD[1]
CANDICE TROCME, PHD[2]
FRANCOISE MOREL, MD, PHD[2]
SERGE HALIMI, MD[1]
PIERRE Y. BENHAMOU, MD, PHD[1]

From the [1]Department of Endocrinology, Pôle Digidune, Centre Hospitalier Universitaire de Grenoble, Grenoble, France; and the [2]Enzymology Laboratory, Department of Cell Biology and Pathology, Centre Hospitalier Universitaire de Grenoble, Grenoble, France.
Corresponding author: Marie Muller, mmuller@chu-grenoble.fr.
DOI: 10.2337/dc09-0770

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

References

1. Liu Y, Min D, Bolton T, Nubé V, Twigg SM, Yue DK, McLennan SV. Increased matrix metalloproteinase-9 predicts poor wound healing in diabetic foot ulcers. Diabetes Care 2009;32:117–119
2. Ladwig GP, Robson MC, Liu R, Kuhn MA, Muir DF, Schultz GS. Ratios of activated matrix metalloproteinase-9 to tissue inhibitor of matrix metalloproteinase-1 in wound fluids are inversely correlated with healing of pressure ulcers. Wound Repair Regen 2002;10:26–37
3. Lobmann R, Zemlin C, Motzkau M, Reschke K, Lehnert H. Expression of matrix metalloproteinases and growth factors in diabetic foot wounds treated with a protease absorbent dressing. J Diabetes Complications 2006;20:329–335
4. Muller M, Trocme C, Lardy B, Morel F, Halimi S, Benhamou PY. Matrix metalloproteinases and diabetic foot ulcers: the ratio of MMP-1 to TIMP-1 is a predictor of wound healing. Diabet Med 2008;25:419–426
5. Lobmann R, Schultz G, Lehnert H. Proteases and the diabetic foot syndrome: mechanisms and therapeutic implications. Diabetes Care 2005;28:461–471