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Reduced TIMP3 expression in ischemic but not neuropathic ulcers from patients with Type 2 Diabetes

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The diabetic foot ulcer is a common complication of diabetes mellitus due to its high frequency and difficulty of complete healing. Peripheral neuropathy, vascular insufficiency, and diminished immune response are major factors in the development of skin ulceration and infection. Elevated levels of matrix metalloproteinases (MMPs) and reduced levels of their endogenous tissue inhibitors (TIMPs) have been shown in chronic wounds, including diabetic foot lesions.Tissue inhibitor of metalloproteinase3 (TIMP3), is a natural inhibitor of MMPs, such as MMP2 and MMP9 and has been shown to have also biological properties independent of MMP-inhibitory activity, including inhibition of angiogenesis, induction of apoptosis and regulation of inflammatory signals. Since TIMP3 is reduced in inflammatory metabolic disorders such as type 2 diabetes mellitus (T2DM) and atherosclerosis, in the current study our aim was to assess the role of TIMP3 and its targets in neuropathic and ischemic diabetic foot ulcers by analyzing biopsy samples. Methods-Patients and biopsies: We recruited 40 patients with type 2 diabetes and foot ulcer graded according to Texas Wound Classification (TWC).Biopsies were obtained under local anesthesia with 2% lidocaine from the border area of the ulcer and distinguished, with respect to underlying causes, in associated with neuropathy (TWC class A = neuropathic ulcer n=19) or peripheral vascular disease (TWC class C = ischemic ulcer n=21). For each biopsy were measured MMP-2 (gelatinase A) and MMP-9 (gelatinase B), were obtained Total RNA and single-strand ,was determined TACE activity. Another class of Metalloprotease,the A Disintegrin and A MetalloProtease Domain (ADAM) might be involved in the wound healing process. Results: We examined whether foot ischemia or neuropathy promote different activation in MMP enzymes in subjects with diabetic foot ulcer. Zymography analysis showed a significant increase in MMP9 activity in ischemic compared to neuropathic biopsies ($p<0.05$). In contrast, there was no differencein MMP2 activity and in the pro-MMP2 and pro-MMP9 levels, indicating a specific upregulation of MMP9 active form. We found that ischemic ulcers exhibited increased ADAM17/TACE activity compared to neuropathic ulcers ($p<0.05$) and only TIMP3 expression was lower in ischemic compared to neuropathic samples ($p<0.05$).The data suggest that the TIMP3 reduction specifically in ischemic ulcers may represent a causative factor in the ulcer progression and a target in the treatment of chronic wounds.