# Impaired integration of endothelial progenitor cells in capillaries of diabetic wounds is reversible with vascular endothelial growth factor infusion

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**To understand impaired angiogenesis in diabetic wounds, polyvinyl tubes were implanted subcutaneously in rats to form a granulation tissue for 2 weeks and the granulation tissue was studied after inducing diabetes with streptozotocin. By 1 week of diabetes, the granulation tissue was bloody and thinner than controls, its medial layer was depleted of microvessels, and the surviving vessels appeared dehisced. Vascular endothelial growth factor (VEGF) in the diabetic granulation tissue was reduced by 50% compared with control granulation tissue. After 3 days of diabetes, the diabetic tissue showed a greater degree of apoptosis in the microvessels. Chemotactic factors (stromal cell-derived factor-1α and chemokine receptor-4 (CXCR-4)), responsible for attracting bone marrow cells, showed equal intensity in control and diabetic tissues. As expected, progenitor endothelial CD-34 cells were observed in abundance in both the control and the diabetic granulation tissues. However, although the CD-34-positive cells appeared mostly to be integrated in the blood vessels of the control tissue, fewer such cells were present in the blood vessels of the diabetic tissues, suggesting that CD-34 failed to integrate into new blood vessels. Infusion of VEGF in the granulation tissue of diabetic rats for 1 week resulted in complete prevention of the microvascular defect compared with the contralateral granulation tissue that showed the typical diabetic changes. It was concluded that diabetes causes reduction of VEGF in the wound, resulting in loss of blood vessels by apoptosis and possible failure of CD-34 cells to integrate into the vessel structure. (Translational Research 2007;149:282–291)**

**Abbreviations:** CXCR-4 = chemokine receptor-4; CD-34 (or CD-31) = cluster of differentiation (cell marker)-34 (or -31); FITC = fluorescein isothiocyanate; SDF-1α = stromal cell-derived factor-1 alpha; STZ = streptozotocin; TUNEL = terminyl deoxynucleotidyl transferase biotin-dUTP nick end labeling; VEGF = vascular endothelial growth factor

Diabetes leads to a generalized microvascular disease that ultimately causes extensive damage to the heart, eye, kidney, and nervous system. The affected vessels undergo either excessive proliferation, as in the eye, or regression and tissue scarring, as in most other tissues.[1] Wound healing is also impaired, largely because of poor new blood vessel formation (angiogenesis).[2,3]

In normal wound healing, angiogenesis takes place to supply blood to the newly formed healed tissue. This

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