

Topical simvastatin shown to accelerate wound healing in diabetes

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Delayed wound healing is a major complication of diabetes because the physiological changes in tissues and cells impair the wound healing process. This can result in additional disease outcomes such as diabetic foot ulcer, a significant cause of morbidity in the growing population of diabetic patients. A new study has found that topically applied simvastatin accelerates wound healing in diabetic mice, suggesting important implications for humans with diabetes. This study is published in the December issue of *The American Journal of Pathology*.

The research was performed by scientists at the Departments of Dermatology and Ophthalmology of Kyoto Prefectural University School of Medicine, Kyoto, Japan; the Department of Dermatology at Hamamatsu University School of Medicine, Hamamatsu, Japan; and Shiseido Innovative Scientific Research Center, Yamamoto, Japan.

"We know that there are several factors involved in delayed [wound healing](#) in diabetes," says lead investigator Jun Asai, MD, PhD. "These factors include more rapid apoptosis (cell death) and reduced angiogenesis (growth of new blood vessels). Impaired lymphangiogenesis, or formation of new [lymphatic vessels](#), has also recently been established as a major factor."

Recent studies have shown that statins have uses beyond their cholesterol-lowering effects and can stimulate the growth of new blood vessels when used systemically. This study tested whether topical application of simvastatin could promote angiogenesis and lymphangiogenesis during

wound healing in genetically [diabetic mice](#). An advantage of topical application is that a suitable concentration of simvastatin can be applied without risk of serious systemic effects such as [kidney damage](#).

The investigators generated a full-thickness skin wound on the backs of diabetic mice. Each wound was treated with a topical application of either simvastatin in petroleum jelly or petroleum jelly alone. The application was repeated on days four, seven, and ten.

After two weeks, the simvastatin-treated wounds were more than 90% healed, whereas less than 80% were healed in the wounds treated by petroleum jelly alone. The difference in wound closure was greatest on day seven when the simvastatin-treated wounds were 79.26% healed compared with 52.45% in the control group.

"Our results suggested to us that the mechanisms underlying the lymphangiogenic effects of simvastatin in lymphatic endothelial cells (LECs) might be similar to those for angiogenic effects," comments Dr Asai. "However, contrary to our expectation, simvastatin did not promote proliferation of human LECs in vitro. We therefore investigated other possible sources of lymphangiogenic factors."

Earlier reports suggested that infiltrating macrophages contribute to lymphangiogenesis as the major producer of vascular endothelial growth factor C (VEGF-C) in cutaneous wound healing. In this study, the number of infiltrating macrophages in granulation tissue was significantly increased by [topical application](#) of simvastatin, and most of these macrophages produced VEGF-C.

"This study shows that topical simvastatin significantly accelerates wound recovery by increasing both angiogenesis and lymphangiogenesis. Our observations suggest that the favorable effects of [simvastatin](#) on lymphangiogenesis are due both to a direct influence on lymphatics and

indirect effects via macrophages homing to the wound. This is a simple strategy that may have significant therapeutic potential for enhancing wound healing in patients with impaired microcirculation, such as that in diabetes. Further investigation is needed to determine its clinical utility", concludes Dr Asai.

More information: "Topical simvastatin accelerates wound healing in diabetes by enhancing angiogenesis and lymphangiogenesis," by Jun Asai, Hideya Takenaka, Satoshi Hirakawa, et al. ([dx.doi.org/10.1016/j.ajpath.2012.08.023](https://doi.org/10.1016/j.ajpath.2012.08.023)). It appears in *The American Journal of Pathology*, Volume 181, Issue 6 (December 2012)

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