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Skin patch could help heal, prevent diabetic ulcers, study finds

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Researchers at the Stanford University School of Medicine say they have developed a safe and effective skin patch to deliver a drug that enhances the healing of diabetes-related ulcers. The patch, which they tested in mice, may also serve as a way to prevent ulcer formation.

Among the more than 29 million people in the United States with either type-1 or type-2 diabetes, an estimated 15 percent develop ulcers. The ulcers, sores or open wounds that usually occur on the foot, become a secondary health condition that leads to prolonged disability, high rates of recurrence and increased mortality. Nonhealing wounds related to diabetes are the leading cause of nontraumatic amputations in the country.

What causes these ulcers has been known for several years. In 2009, researchers led by Geoffrey Gurtner, MD, a professor of surgery at Stanford, and a group of scientists at the Albert Einstein College of Medicine published a study pinpointing exactly how diabetes reduces the ability of tissue to form new blood vessels essential for wound healing: High levels of blood sugar compromise the body's ability to grow the new blood vessels. That same study found a potential treatment: deferoxamine, or DFO, a drug already approved by the Food and Drug Administration to treat hemochromatosis, a condition in which too much iron accumulates in the body. DFO can correct the diabetes-impaired expression of a protein that supports new vascular growth.

The problem was how to deliver the DFO, which would be toxic if used

for as long as diabetic pressure ulcers can take to heal. So the researchers decided to investigate an alternative: local delivery of just enough medication directly to an ulcer through a patch applied to the skin.

Dominik Duscher, MD, a postdoctoral scholar in surgery, and Evgenios Neofytou, MD, an instructor at the Stanford Cardiovascular Institute, share lead authorship of a paper describing the findings of the new research. Gurtner is the senior author. The paper will be published online Dec. 22 in the *Proceedings of the National Academy of Sciences*.

Challenges of developing a patch

Developing the skin patch raised a set of formidable challenges, which the Stanford team took on, step by step, working with materials engineers led by co-author Jayakumar Rajadas, PhD, director of Stanford's Biomaterials and Advanced Drug Delivery Laboratory.

The DFO needed to be modified to penetrate the outermost layer of the skin to activate the formation of new blood vessels, but its release also needed to be controlled to prolong the availability of the DFO at a therapeutic level. It took nearly four years of attempts before the team produced a solution: Envelope the DFO with a surfactant, which would lower the DFO's natural surface tension and transform its molecules into microparticles that could penetrate the skin, then embed them in a pliable polymer matrix, a couple of millimeters thick, that would protect the fragile DFO microparticles and disperse them gradually as the matrix disintegrated.

"The mice tolerated it very well," Duscher said, which could bode well for humans. Once the patch is applied—the moisture in skin makes a natural adherent—the diffusion of the DFO begins and its molecules are drawn into the wounded tissue and skin.

'Hope to start clinical trials soon'

Not only did the wounds in the mice heal more quickly, Duscher said, but the quality of the new skin was even better than the original. The researchers also used the DFO matrix on a mouse with diabetes to see if it would prevent ulcer formation—and it did. "We were very excited by the results," Duscher said, "and we hope to start clinical trials soon to test this in humans."

"This same technology is also effective in preventing pressure ulcers, which are a major source of morbidity and mortality in patients with neurologic injury or the elderly," said Gurtner, who is also the Johnson & Johnson Distinguished Professor in Surgery II. "The actor Christopher Reeve actually died from a pressure ulcer and not his spinal cord injury, which really emphasizes the extremely limited therapeutic options for these patients."

More information: Transdermal deferoxamine prevents pressure-induced diabetic ulcers, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1413445112

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