

Could type 2 diabetes be managed with a simple outpatient procedure?

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Gregory Ginsberg, a Penn Medicine doctor, is exploring a new frontier in the treatment of type 2 diabetes.

He's co-leading a clinical trial at Penn that is testing whether killing cells on the inner surface of the duodenum—the first part of the small intestine immediately past the stomach—can lead to better control of blood sugar in people with [diabetes](#).

Preliminary work done in South America and Europe has found that the outpatient, [endoscopic procedure](#) called duodenal mucosal resurfacing (DMR) reduced A1C, a long-term measure of blood sugar; reduced the need for insulin; and reduced liver fat in people with [nonalcoholic fatty liver disease](#). While not a cure, the procedure could allow patients with diabetes to take fewer drugs and is another sign, Ginsberg said, that cells in the duodenum play an important role in the body's metabolic communication system.

Penn is now one of five U.S. institutions participating in a small pilot study of the procedure. Results are not yet available, but Ginsberg said the previous research has made him hopeful that he is studying a "transformative" procedure.

"This research is compelling because it harnesses the untapped potential of the luminal digestive tract in the management of health and disease," Ginsberg said. "Moreover, it is provocative in its application of minimally invasive endoscopic therapy to treat a metabolic condition."

The procedure had its genesis in observations about the impact of gastric bypass surgery, which creates a new path for partially digested food that bypasses the duodenum entirely. Obese patients who are diabetic and undergo the procedure often see big improvements in markers of diabetes even before they lose a lot of weight, Ginsberg said. That has triggered interest in whether the duodenum is involved in signaling other parts of the body about the need for insulin, a hormone involved in allowing your cells to use blood sugar for energy. It's part of a relatively new avenue of research into the role the gut plays in metabolism.

"The gut is really a frontier in diabetes research," said Raymond Soccio, a Penn endocrinologist who studies fatty liver disease and is not involved in the study.

In type 2 diabetes, cells develop insulin resistance, which means they don't respond properly to the hormone. (In the much less common type 1, an autoimmune condition, the body stops making insulin.) Insulin resistance is an important factor in type 2 diabetes, nonalcoholic fatty liver disease—most obese people with type 2 have this—and polycystic ovary syndrome (PCOS).

Soccio said bile acids, which are involved in the absorption of fat and fat-soluble vitamins, cycle between the duodenum and the liver. "They also seem to have important signaling and other functions in the liver related to diabetes and insulin resistance that we don't fully understand," he said.

Ginsberg said that cells in the duodenum become enlarged and dysfunctional after years of exposure to unhealthy diets rich in fat and sugar. DMR uses a catheter to deliver a balloon filled with 176-degree water to the duodenum. During the 60-minute procedure, Ginsberg uses the balloon to ablate or burn cells in segments over four inches of the duodenum. The hypothesis is that, when they grow back, the cells send more normal metabolic signals, Ginsberg said.

Patients in the study's control group undergo a sham procedure that includes everything but the heated water.

The catheter was developed by Fractyl Laboratories Inc., in Lexington, Mass. Its studies abroad are looking at the impact of the procedure on diabetes, fatty liver disease and PCOS. The company has approval to begin marketing its procedure in Europe, said Harith Rajagopalan, Fractyl's co-founder and CEO. It announced Jan. 28 that the procedure would first become commercially available in the United Kingdom as

part of a partnership with HCA Healthcare UK.

A cardiologist who earned a doctorate studying the genetics of colon cancer, Rajagopalan wondered why so many of his heart patients had diabetes. He also had a personal interest in the disease because his father had it. When he and his co-founder saw what [bariatric surgery](#) could do for diabetes, they thought that "insulin resistance may be a disease of the gut lining," he said. About 10 years ago, they began exploring the idea that the gut lining could be renewed in much the way that a chemical peel can make your skin look younger.

He sees Fractyl's research as "starting to pull a thread" that connects diseases that have, until recently, largely been studied and treated separately.

Results released last year from studies abroad showed the procedure is not a cure. One study found that average A1C, a measure of average blood sugar over three months, dropped from 8.5% to 7.5% after two years. Normal is less than 5.7%. Another small study found that 13 of 16 patients were able to stop taking insulin. While the reduction in A1C seems small, Rajagopalan said it is enough to avoid taking a third drug and to significantly reduce the risk of problems associated with diabetes-related damage to small blood vessels, and issues such as kidney failure, eye disease, and peripheral neuropathy.

Studies also found reductions in liver fat of 32% to 45% after the procedure. There are currently no drug treatments for fatty liver disease, Rajagopalan said. The reduction from DMR is about what most medications currently being tested are shooting for and "very few are actually attaining."

Rohit Soans, a bariatric surgeon at Temple University Hospital who is not involved in DMR research, said bypass surgery typically has much

greater impact. The procedure cures diabetes in 83% of patients, he said, and reduces [liver fat](#) by almost 90%. "The effect on diabetes is literally almost magical," he said.

But he still found the Fractyl results "pretty promising." Insurance companies make it hard for patients to qualify for bariatric surgery, he said, so some patients might welcome a less invasive alternative. He wants to see longer-term data on results and safety. He pointed out that half of patients in a DMR study published last year had side effects, most considered mild.

Penn has so far attracted only three patients to the trial. The goal for all five centers is 18. To be eligible, patients must have poorly controlled diabetes despite being on metformin and one other drug. They can't be taking insulin. Their body mass index needs to be between 28 and 40 and they must be under age 65.

Anastassia Amaro, medical director of Penn Metabolic Medicine and principal investigator for the trial at Penn, said the "extremely strict" rules have slowed recruitment.

"There is huge interest from patients and people with diabetes," she said. "We receive phone calls daily."

She is intrigued by the results from other countries and the "out-of-the-box thinking" of the investigators.

Soccio also said DMR is "promising" and he'd like to know more about how it works. As a clinician, he wonders which patients will benefit most from it. There are many medications for diabetes, he said, and most people can get it under control. It can be a lot of work, though, and some may like the idea of a procedure that works for months or years. "That would appeal to some people," he said.

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