

Type 2 diabetes may be caused by intestinal dysfunction

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Growing evidence shows that surgery may effectively cure Type 2 diabetes -- an approach that not only may change the way the disease is treated, but that introduces a new way of thinking about diabetes.

A new article -- published in a special supplement to the February issue of *Diabetes Care* by a leading expert in the emerging field of diabetes surgery -- points to the small bowel as the possible site of critical mechanisms for the development of diabetes.

The study's author, Dr. Francesco Rubino of New York-Presbyterian Hospital/Weill Cornell Medical Center, presents scientific evidence on the mechanisms of diabetes control after surgery. Clinical studies have shown that procedures that simply restrict the stomach's size (i.e., gastric banding) improve diabetes only by inducing massive weight loss. By studying diabetes in animals, Dr. Rubino was the first to provide scientific evidence that gastrointestinal bypass operations involving rerouting the gastrointestinal tract (i.e., gastric bypass) can cause diabetes remission independently of any weight loss, and even in subjects that are not obese.

"By answering the question of how diabetes surgery works, we may be answering the question of how diabetes itself works," says Dr. Rubino, who is a professor in the Department of Surgery at Weill Cornell Medical College and chief of gastrointestinal metabolic surgery at New York-Presbyterian/Weill Cornell.

Dr. Rubino's prior research has shown that the primary mechanisms by which gastrointestinal bypass procedures control diabetes specifically rely on the bypass of the upper small intestine -- the duodenum and jejunum. This is a key finding that may point to the origins of diabetes.

"When we bypass the duodenum and jejunum, we are bypassing what may be the source of the problem," says Dr. Rubino, who is heading up NewYork-Presbyterian/Weill Cornell's Diabetes Surgery Center.

In fact, it has become increasingly evident that the gastrointestinal tract plays an important role in energy regulation, and that many gut hormones are involved in the regulation of sugar metabolism. "It should not surprise anyone that surgically altering the bowel's anatomy affects the mechanisms that regulate blood sugar levels, eventually influencing diabetes," Dr. Rubino says.

While other gastrointestinal operations may cure diabetes as an effect of changes that improve blood sugar levels, Dr. Rubino's research findings in animals show that procedures based on a bypass of the upper intestine may work instead by reversing abnormalities of blood glucose regulation.

In fact, bypass of the upper small intestine does not improve the ability of the body to regulate blood sugar levels. "When performed in subjects who are not diabetic, the bypass of the upper intestine may even impair the mechanisms that regulate blood levels of glucose," says Dr. Rubino. In striking contrast, when nutrients' passage is diverted from the upper intestine of diabetic patients, diabetes resolves.

This, he explains, implies that the upper intestine of diabetic patients may be the site where an abnormal signal is produced, causing, or at least favoring, the development of the disease.

How exactly the upper intestine is dysfunctional remains to be seen. Dr. Rubino proposes an original explanation known in the scientific community as the "anti-incretin theory."

Incretins are gastrointestinal hormones, produced in response to the transit of nutrients, that boost insulin production. Because an excess of insulin can determine hypoglycemia (extremely low levels of blood sugar) -- a life-threatening condition -- Dr. Rubino speculates that the body has a counter-regulatory mechanism (or "anti-incretin" mechanism), activated by the same passage of nutrients through the upper intestine. The latter mechanism would act to decrease both the secretion and the action of insulin.

"In healthy patients, a correct balance between incretin and anti-incretin factors maintains normal excursions of sugar levels in the bloodstream," he explains. "In some individuals, the duodenum and jejunum may be producing too much of this anti-incretin, thereby reducing insulin secretion and blocking the action of insulin, ultimately resulting in Type 2 diabetes."

Indeed, in Type 2 diabetes, cells are resistant to the action of insulin ("insulin resistance"), while the pancreas is unable to produce enough insulin to overcome the resistance.

After gastrointestinal bypass procedures, the exclusion of the upper small intestine from the transit of nutrients may offset the abnormal production of anti-incretin, thereby resulting in remission of diabetes.

In order to better understand these mechanisms, and help make the potential benefits of diabetes surgery more widely available, Dr. Rubino calls for prioritizing research in diabetes surgery. "Further research on the exact molecular mechanisms of diabetes, surgical control of diabetes and the role played by the bowel in the disease may bring us closer to the

cause of diabetes."

Today, most patients with diabetes are not offered a surgical option, and bariatric surgery is recommended only for those with severe obesity (a body mass index, or BMI, of greater than 35kg).

"It has become clear, however, that BMI cut-offs can no longer be used to determine who is an ideal candidate for surgical treatment of diabetes," says Dr. Rubino.

"There is, in fact, growing evidence that diabetes surgery can be effective even for patients who are only slightly obese or just overweight. Clinical trials in this field are therefore a priority as they allow us to compare diabetes surgery to other treatment options in the attempt to understand when the benefits of surgery outweigh its risks. Clinical guidelines for diabetes surgery will certainly be different from those for bariatric surgery, and should not be based only on BMI levels," he notes.

"The lesson we have learned with diabetes surgery is that diabetes is not always a chronic and relentless disease, where the only possible treatment goal is just the control of hyperglycemia and minimization of the risk of complications. Gastrointestinal surgery offers the possibility of complete disease remission. This is a major shift in the way we consider treatment goals for diabetes. It is unprecedented in the history of the disease," adds Dr. Rubino.

Type 2 diabetes, which accounts for 90 to 95 percent of all cases of diabetes, is a growing epidemic that afflicts more than 200 million people worldwide.

At a time when diabetes is growing epidemically worldwide, Dr. Rubino says that finding new treatment strategies is a race against time. "At this

point, missing the opportunity that surgery offers is not an option."

Source: New York- Presbyterian Hospital

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