

New Procedures Provide Clues to Surgery's Effect on Diabetes

Focus on Lower Intestine; Redefining the Disease As Curable?

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New York—Novel surgical strategies are elucidating how and why gut hormones play such a surprisingly profound role in the development and reversal of metabolic disorders, according to presentations at the first World Congress on Interventional Therapies for Type 2 Diabetes.

Beyond the traditional lap band or Roux-en-Y gastric bypass (RYGB), surgeons are investigating the hormonal effects on weight and glucose regulation of duodenal-jejunal bypass, ileal interposition and an endoscopically implanted barrier that blocks nutrient absorption in the duodenum and proximal jejunum.

What the three investigational procedures have in common with RYGB is that they all result in a sharp increase in nutrients delivered to the lower intestine, a site of potent hormone secretion. The effects of those hormones on appetite and glucose regulation are so powerful that they might, in the view of some experts, form the basis for actually curing diabetes rather than merely slowing its progression, as do current medical therapies.

"Surgery might actually be fixing what is broken," said the organizer of the meeting, Francesco Rubino, MD, chief of gastrointestinal metabolic surgery at Weill Cornell Medical College in New York City, who is heading up the first academically based diabetes surgery center at that institution. "Diabetes is rarely forced into remission through medical treatment and usually comes at the expense of continuing effort and treatment. Surgery offers the promise of enduring remission with a single procedure. It is something we have never seen in the history of diabetes. It questions the definition of diabetes as a chronic, progressive, irreversible illness. It raises the question for the first time: Can we go beyond treating diabetes to curing it?"

It is not only surgeons who are beginning to view the actions of the lower intestine as fundamental to the development of type 2 diabetes. In the view of David Cummings, MD, associate professor of medicine and deputy director of the Diabetes Endocrinology Research Unit at the University of Washington in Seattle, "There is a great deal of evidence for something special going on in the lower intestine that has a unique effect on blood sugars."

Lower Intestinal Theory

In a review of the recent literature in support of what he called the "lower intestinal theory," Dr. Cummings described one of the early seminal papers by Dr. Rubino in the *Annals of*

Surgery (2004;239:1-11). The key question that Dr. Rubino sought to answer in the study was whether the resolution of diabetes that often follows bariatric surgery occurs because of weight loss or as a direct result of duodenal-jejunal exclusion. Using Goto-Kakizaki rats, a spontaneous nonobese model of type 2 diabetes, he compared the effects of gastrojejunal bypass (with preservation of an intact gastric volume) with a sham operation. Three weeks after surgery, despite no difference in weight between the two groups, the rats that underwent the gastrojejunal bypass had significantly improved glucose tolerance—better than could be achieved with a draconian diet or medication.

Human data in support of the lower intestinal theory have been accumulating quickly. A paper by Judith Korner, MD, PhD, assistant professor of clinical medicine and director of the Medical Weight Control Center at Columbia University College of Physicians and Surgeons in New York City, found an increased level of glucagon-like peptide-1 (GLP-1) and blunted glucose-dependent insulinotropic peptide secretion following RYGB in 13 patients but not following gastric banding in 10 patients (*Surg Obes Relat Dis* 2007;3:597-601).

At the international diabetes meeting, Dr. Korner told the audience, "In some unpublished data, we have looked at the banded versus bypass patients. If you follow them from preoperatively to one year postoperatively, the degree of insulin resistance correlates to weight loss in the banded patients, but in the bypass patients, there is no correlation at all."

Treating Nonobese Diabetics

Fundamental to the very notion of interventional therapies aimed specifically at diabetes rather than at obesity, is that the procedures should work in patients who are not morbidly obese. A recent paper by Wei-Jei Lee, MD, of National Taiwan University (*J Gastrointest Surg* 2008;12:945-952), confirmed that point. Among 201 patients who underwent a laparoscopic mini-gastric bypass, 44 (21.9%) had a body mass index (BMI) of less than 35, while the remainder had a BMI of 35 or more. One year after surgery, fasting plasma glucose returned to normal in 89.5% of those with a BMI of less than 35, compared with 98.5% of those with a higher BMI. The treatment goal of achieving an A_{1c} (glycated hemoglobin) of less than 7%, low-density lipoprotein less than 150 mg/dL and triglycerides less than 150 mg/dL was met in 76.5% of patients with a BMI below 35 and 92.4% of those with a higher BMI. Thus, Dr. Lee concluded, patients with a BMI below the standard cutoff for bariatric surgery had a rate of resolution of their diabetes only slightly less than that of their heavier counterparts.

To find out how many surgeons are already conducting bariatric procedures in patients with a BMI under 35, Dr. Rubino said that he is conducting a worldwide survey. So far, he said, he had received information on 237 patients, the majority of whom had undergone a gastric bypass. "Almost every one of these produced improvement in hyperglycemia," Dr. Rubino said. "When you look at A_{1c}, there is greater efficacy in patients who had a bypass, similar to what we've been seeing in patients with more obesity. Some of the patients were able to suspend taking diabetic medications following surgery, others not completely."

Bringing Back Ileal Interposition

Dr. Cummings spoke at length during his presentation about a procedure first described in the early 1950s and since revived by Dr. Rubino and others: the so-called ileal interposition, in which no part of the stomach or intestines is removed or constricted; instead, the only change is that a piece of ileum is moved up.

"It is not a malabsorptive procedure, not a constrictive procedure," Dr. Cummings said. "You see a big rise in GLP-1 levels. It results in a reduction in body weight and food intake, despite no change in absorption. And early evidence suggests there may be an increase in beta-cell mass following the procedure. That would be a cool thing, because it would show you could actually reverse the disease process."

Noninvasive Means to the Same End

Yet with only an estimated 1% of morbidly obese patients undergoing bariatric surgery as it is, surgeons and endocrinologists at the meeting felt compelled to consider the possibility of extending the benefits of surgery without making a single incision.

Lee Kaplan, MD, PhD, associate professor of medicine and associate chief of research in the Division of Gastroenterology at Harvard Medical School in Boston, described his research with the EndoBarrier gastrointestinal liner, an impermeable device that is implanted during an outpatient procedure in the upper intestine via the mouth to block absorption of nutrients.

Dr. Kaplan described a trial, not yet published, in which 19 patients with type 2 diabetes either received the liner or underwent a sham endoscopy. Twelve weeks after implantation, patients who received the liner experienced "a significant decrease in A_{1c} ," he said, compared with patients who underwent the sham procedure. "By 30 weeks, there was a 2.9% decrease of A_{1c} on average."

Dr. Kaplan said that 118 of the devices have been implanted in patients in trials in Chile, the Netherlands and the United States. "Different types of trials have been done, but the data in humans so far look like the well-controlled data in rats," he said.

Because the EndoBarrier is removable, "it offers the same kind of possibilities as medical treatment," said Jan Willem Greve, MD, PhD, professor of surgery and program director of bariatric surgery at Maastricht University Medical Center in the Netherlands.

"You can take the device out if the patient doesn't want to go on," Dr. Greve said. "It gives us a really good opportunity to do a trial. That's what we're going to do next."

Moving Forward

Although some meeting attendees urged caution in applying the lessons of research outside the realm of clinical trials, others expressed frustration at the notion of withholding interventional treatments from diabetics who could benefit from them now.

"I'm just worried we are procrastinating on finding the absolute ideal mechanism of action before we go in and encourage surgery," said Tessa van der Merwe, MB, ChB, PhD, honorary professor of endocrinology at the University of Pretoria and director of Netcare Bariatric Centres of Excellence in Parktown, South Africa. "I'm concerned that we're waiting for that one ideal trial that is going to come around in 10 years and provide us with all the data."

Novel Surgical Procedures For Diabetes

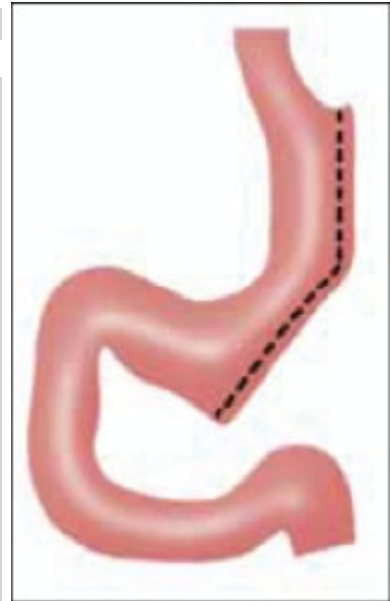


Duodenal-Jejunal Bypass (DJB)

First described as an experimental anti-diabetic procedure by Francesco Rubino, MD, chief of Gastrointestinal Metabolic Surgery and assistant professor of surgery at Weill Cornell Medical College in New York City, DJB consists of a stomach-sparing bypass of a short segment of proximal small intestine, equivalent to the amount of intestine bypassed in a standard Roux-en-Y gastric bypass. The duodenum and the proximal segment of jejunum are excluded from the transit of nutrients. Two variants of DJB have been performed: One includes preservation of the pylorus and a duodeno-jejunal anastomosis; alternatively, a pre-pyloric gastrojejunostomy can be performed.

Sleeve Gastrectomy (SG)

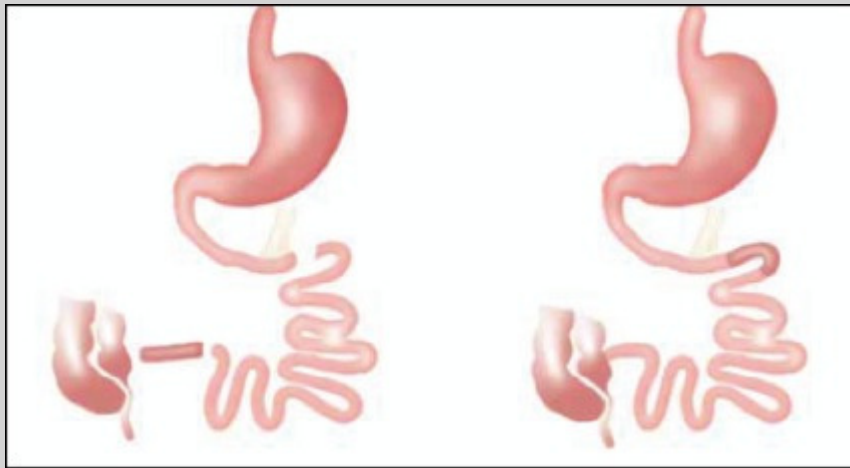
To shorten the duration of the laparoscopic biliopancreatic diversion with duodenal switch in high-risk patients, Michel Gagner, MD, currently chairman of the Department of Surgery at Mount Sinai Medical Center in Miami Beach, Fla., proposed a two-stage procedure, starting with sleeve gastrectomy, followed by duodenoileostomy and ileo-ileostomy a few months later. This modality resulted in a drastic reduction of morbidity and mortality compared to the traditional one-stage approach in super-superobese patients (BMI>60). In addition to reducing the capacity of the stomach, the procedure eliminates the ghrelin-rich gastric fundus, which may play a role in its mechanism of action.



Ileal Interposition (IT)

During IT, a small segment of ileum—with its vascular and nervous supplies intact—is surgically interposed into the proximal small intestine, where its exposure to ingested nutrients is greatly increased. Animals with IT show exaggerated GLP-1 and peptide YY responses to nutrient loads. These hormonal changes are associated with reductions in food

intake, body weight and improved glucose homeostasis, without restriction and malabsorption.



Photos/descriptions adapted from program book for the First World Congress on Interventional Therapies for Type 2 Diabetes, Gastrointestinal Procedures, pages 58-59.