

# Insulin, C-Peptide Levels Increase

GI Surgery from page 1

type 2 diabetes, especially in regard to the decline of glucagon-like peptide 1 (GLP-1) and resistance to glucose-dependent insulinotropic peptide (GIP), said Dr. DePaula of the department of surgery at Hospital de Especialidades, Goiânia, Brazil.

Based on the pathophysiologic mechanisms of type 2 diabetes, Dr. DePaula and his coinvestigators designed the procedures to address the following objectives:

- ▶ Early exposure of ingested nutrients to the transposed ileum, which may allow an early rise of GLP-1, to increase the effect of early-phase insulin secretion.

- ▶ Correcting the defective amplification of the late-phase plasma insulin response to glucose by GIP.

- ▶ Diminishing or abolishing the stimulation of the duodenum by bypassing it with a diverted sleeve gastrectomy.

- ▶ Decreasing insulin resistance in peripheral tissues.
- ▶ Caloric restriction.
- ▶ Weight loss.
- ▶ Resolution or control of diabetes-related comorbidities.

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In one study, the investigators monitored the hormonal profile of 58 patients with type 2 diabetes who underwent a laparoscopic sleeve gastrectomy.

In 30 patients, the investigators interposed a 150- to 170-cm segment of ileum into the proximal jejunum about 20 cm beyond the ligament of Treitz; this was the standard version of the procedure.

The other 28 patients had a similar length of ileum interposed into the proximal duodenum, bypassing the second, third, and fourth parts of the duodenum; this was the

diverted version of the procedure.

The patients had a mean body mass index of 28 kg/m<sup>2</sup> (range, 20-34.8), and a mean age of about 51 years. They had had diabetes for a mean duration of nearly 10 years (range, 3-22 years).

All patients had a hemoglobin A<sub>1c</sub> level of at least 7.5% for the previous 3 months and had been using oral antidiabetic agents and/or insulin for at least the previous year. Nearly 40% of the patients were using insulin.

**'These are truly experimental procedures and they should be done only within the context of an IRB.'**

DR. SCHAUER



Among all the patients, average HbA<sub>1c</sub> levels improved significantly from 8.9% at baseline to 5.8% after a mean follow-up of 19 months. Overall, 65% of patients went into diabetes remission, defined as an HbA<sub>1c</sub> less than 6%, whereas another 27% achieved an HbA<sub>1c</sub> between 6% and 7%. The patients experienced significant reductions in mean fasting plasma glucose (from 215 to 105 mg/dL) as well as plasma glucose 2 hours after a mixed-nutrient 420-kcal meal (from 266 to 133 mg/dL).

Concentrations of triglycerides and LDL cholesterol as well as insulin resistance also declined significantly.

When the patients were tested at 16 months with the 420-kcal meal, Dr. DePaula and his associates found that levels of GLP-1 rose significantly, especially among patients who had undergone the diverted version of the procedure.

Dr. DePaula said that improvement in the level of GLP-1 may be a key factor in initiating the improvement of diabetes after surgery, although he cautioned that it

may be misleading to measure the hormone levels separately because of built-in redundancy between their functions.

By 16 months, levels of GIP, insulin, and C-peptide had increased significantly, whereas levels of leptin and resistin also declined significantly in both groups. No significant changes occurred in concentrations of amylin, somatostatin, interleukin-6, and adiponectin.

At 16 months, both groups showed significant drops in ghrelin levels and an exaggerated increase in peptide YY levels at time points that were different from levels before the operation.

Ghrelin deficiency has been shown to decrease basal insulin levels, enhance glucose-stimulated insulin secretion, and improve insulin sensitivity (J. Clin. Endocrinol. Metab. 2004;89:5035-42).

Dr. DePaula and his colleagues expected that the procedures would decrease glucagon levels, but at 16 months the defective pattern of glucagon output in relation to its preoperative levels had not been corrected.

Patients with type 2 diabetes are known to have attenuated and delayed suppression of glucagon after ingesting glucose. Hyperglycemia in type 2 diabetes is in part caused by an overproduction of glucose from the liver, caused by hyperglucagonemia and increased hepatic output of glucose through glycogenolysis (Diabetes 2000;49:1367-73).

"These hormonal results support the concept that surgery can be part of the solution for a non-morbidly obese type 2 diabetic population through an operation that tries to address our current knowledge of the mechanisms of the pathophysiology of type 2 diabetes," said Dr. DePaula, who disclosed that he is a consultant to Covidien.

Dr. DePaula said that although he and

his colleagues did not compare the two groups, they speculated that the diverted version would be more effective than the standard version because it influences more of the components of the pathophysiologic mechanisms of the disease.

In a second presentation at the meeting, Dr. DePaula examined a larger group of 69 patients who had undergone the diverted version of the operation (including the 28 patients in the other study). These patients had a mean age of 51 years and a mean duration of type 2 diabetes of 11 years. Of the 69 patients, 30 (43%) used insulin therapy.

The patients' average HbA<sub>1c</sub> dropped from 8.7% before the operation to 5.9% after a mean follow-up period of nearly 22 months. Diabetes remission (HbA<sub>1c</sub> less than 6%) occurred in 65%. Another 31% had adequate glycemic control with an HbA<sub>1c</sub> of 6%-7%. Other laboratory values improved significantly over the course of

follow-up, including fasting plasma glucose (from 208 to 102 mg/dL), postprandial glucose (from 305 to 141 mg/dL), triglycerides (from 236 to 106 mg/dL), and LDL cholesterol (from 114 to

82 mg/dL).

Nearly all patients had resolution of macroalbuminuria and/or microalbuminuria. The operation also reduced insulin resistance significantly based on scores derived with the Homeostatic Model Assessment of Insulin Resistance index.

The patients' mean BMI dropped from about 26 to 21. No patients had malnutrition.

In both studies, no patients required conversion to open surgery, and patients stayed in the hospital for a mean of about 3 days. Major postoperative complications occurred in six patients in the first study and in five patients in the second study. No deaths occurred. ■



**'These hormonal results support the concept that surgery can be part of the solution.'**

DR. DEPAULA

# Fetuin-A Found to Be a Novel Risk Factor for Type 2 Diabetes

BY BRUCE JANCIN  
Denver Bureau

COLORADO SPRINGS — Serum fetuin-A level is an independent risk factor for subsequent development of diabetes in the well-functioning elderly, according to results from a case-cohort substudy of 519 elderly subjects randomly selected from a larger longitudinal study.

The burning issue now becomes whether fetuin-A is a modifiable risk factor or simply a marker of increased risk. That remains to be determined in future studies, observed Dr. Joachim H. Ix of the University of California, San Diego.

Fetuin-A is a multifunctional hepatic secretory protein involved in glucose homeostasis. It binds insulin receptors in fat and muscle and, in vitro, inhibits insulin action.

Moreover, the fetuin-A gene keeps interesting company. It is located on chromosome 3C27, which has been mapped as a metabolic syndrome and type 2 diabetes susceptibility locus.

At a conference of the American Heart Association, Dr. Ix presented the case-cohort study involving the 519 ran-

domly selected participants in the National Institutes of Health-sponsored longitudinal Health, Aging, and Body Composition study, which enrolled more than 3,000 well-functioning white and black subjects aged 70-79 years.

All participants in the substudy were without diabetes at entry. During 6 years of follow-up, 135 of them developed new-onset diabetes. The incidence among participants in the lowest quartile for baseline serum fetuin-A was about 7%, roughly half the rate in those in the highest quartile.

After full adjustment for age, gender, race, blood pressure, fasting glucose, physical activity, HDL cholesterol, waist circumference, C-reactive protein, and triglycerides, individuals in the top fetuin-A tertile—that is, greater than 0.97 g/L on a commercial ELISA assay

marketed by Epitope Diagnostics Inc.—had an adjusted 2.4-fold greater risk of developing diabetes than did those in the bottom tertile, with a level of 0.76 g/L or less. Those in the middle tertile had a 1.8-fold increased risk.

Results of this new longitudinal study are consistent with an earlier cross-sectional study in which Dr. Ix and coworkers showed higher fetuin-A was strongly associ-

ated with prevalent metabolic syndrome (Circulation 2006;113:1760-7).

Also relevant is the fact that knockout mice lacking the fetuin-A gene demonstrate greater insulin sensitivity, less weight gain, less adiposity, lower free fatty acids, and lower triglycerides than do mice producing the hepatic protein, Dr. Ix continued.

Dr. Jeremiah Stamler was particularly intrigued by Dr. Ix's earlier work demonstrating an inverse association between fetuin-A levels and mitral annular calcification in patients with coronary heart disease (Circulation 2007;115:2533-9).

This seems contradictory: High levels of fetuin-A independently predict an atherogenic lipid profile, metabolic syndrome, and diabetes, all strongly associated with increased risk of coronary disease, yet high fetuin-A might also protect against valvular and vascular calcification, said Dr. Stamler, professor emeritus of preventive medicine at Northwestern University, Chicago.

Dr. Ix agreed this is an exciting area, but one where the research is still at quite an early stage. It's plausible there is a U-shaped relationship between fetuin-A level and cardiovascular risk, he noted.

Dr. Ix and his associates' study was a finalist for the annual Jeremiah and Rose Stamler Research Award for Young Investigators. ■

**Individuals in the top fetuin-A tertile had an adjusted 2.4-fold greater risk of developing diabetes than did those in the bottom tertile, researchers said.**