gi Dynamics™
Defining Noninvasive Metabolic Control

June 18, 2008

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Lead Analyst
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Office of Clinical Standards and Quality
Centers for Medicare and Medicaid Services
Baltimore, MD
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Re: NCA for Surgery for Diabetes (CAG-00397N)

Dear Dr. Meltzer:

GI Dynamics appreciates the Centers for Medicare and Medicaid Services interest in considering a National Coverage Analysis (NCA) to "assess the nature of the scientific evidence supporting surgery for the treatment of diabetes and whether a NCD is warranted," and the request for comments regarding "clinical studies and other scientific information about the technology under review and the short and long term outcomes."

- We support the surgical community's assertion that there is a significant body of evidence which supports surgical intervention for Type 2 Diabetes. The mechanism of action achieved through surgical bypass of the duodenum and proximal jejunum holds great promise for some patients who are struggling to control Type 2 Diabetes with currently available pharmacological therapy.

- We support the consideration of coverage for surgical intervention to treat selected patients with Type 2 Diabetes based on the current body of literature available.

- We also support the notion that ongoing and future studies may assist in determining the optimal course of therapy and could provide some further validation as to the group of patients most likely to benefit from surgical intervention.

- Finally we would respectfully request, should CMS conclude that a National Coverage Determination is not warranted at this time, that CMS allow the current process to continue through local discretion as additional studies provide additional supportive data.

We believe that the supporting data are convincing, and that the mechanism of action that results from surgical bypass may be the only hope for some patients with advanced Type 2 Diabetes to achieve remission of the disease.

We are studying this mechanism, and are developing a new technology that may one day soon demonstrate the ability to replicate the mechanism of action of surgery, but do so in a non-invasive, non-surgical approach.

GI Dynamics is a medical device company that is developing and studying this promising technology, called the EndoBarrier™, as a non-invasive, endoscopic procedure for treating Type 2 Diabetes and Obesity. We are currently in clinical trials in the U.S., Europe, and South America (See Appendix 1).

Remission of Diabetes Observed in Duodenal Bypass (surgical or mechanical)

Surgical bypass of the duodenum and proximal jejunum in association with roux en y gastric bypass surgery appears to result in a cascade of neurohormonal responses which cause rapid normalization of glucose homeostasis, and resolution or remission of Type 2 Diabetes. This procedure also results in weight loss, which is an essential component of reducing insulin resistance and achieving successful Type 2 Diabetes control.

The EndoBarrier™ is delivered and removed endoscopically, and creates a mechanical bypass of the duodenum and proximal jejunum. Early clinical results, similar to the effects of bypass surgery, have demonstrated rapid normalization of glucose homeostasis and weight loss. The fact that glucose homeostasis is achieved prior to weight loss is particularly interesting, and may be further evidence that the Diabetes remission is an independent phenomenon that may be the direct result of duodenal bypass (Tarnoff, M, et al, Interim Report on a Prospective, Randomized Sham Controlled Trial Investigating a Completely Endoscopic Duodenal-Jejunal Bypass Sleeve for the Treatment of Type 2 Diabetes, presented at ADA 2008).

Challenges of Currently Available Treatments

Type 2 Diabetes is a progressive disease. Current medical treatments have been largely unsuccessful in providing short or long term control (Gæde, P et al, Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes, NEJM, January 30, 2003). Most treatment involves some combination of diet and exercise, followed by or combined with a progression of pharmaceutical therapies. These drugs, while effective for short periods of time, do not stop the progression of Diabetes. Many have side effects that exacerbate the problem by causing weight gain, which increases insulin resistance and causing further disease progression.

Additionally, the current treatments do not provide adequate glucose control. Some patients, even under the most rigorous supervision, experience dramatic fluctuations in blood sugar levels which ultimately result in deterioration of microvasculature systems and result in damage to kidneys, nerves, eyes, and the cardiovascular system.

The end result of this suboptimal treatment for many people is blindness, end-stage renal disease, amputation, heart-attack and stroke. The Centers for Disease Control and the American Diabetes Association track the significant national healthcare and financial impact of Diabetes (CDC, National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2005. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2005).

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Why Surgery Makes Sense

The metabolic effects of gastric bypass surgery have been recognized for decades. The first reported observation dates back to 1955 when surgeons observed the rapid remission of type 2 diabetes in patients who underwent hemigastrectomy and duodenal bypass reconstruction (Friendman NM, et. Al. *Surgery, Gynecology & Obstetrics; February 1955*). Numerous peer reviewed publications have since emerged detailing the direct ability of gastric bypass to rapidly normalization glucose tolerance. While additional specific data and studies are warranted, new surgical approaches have shown solid results and excitement has risen in the endocrinology community. For example, the Diabetes Surgery Summit, which took place on March 28-31, 2007, in Rome, Italy, concluded that "gastrointestinal surgery may be appropriate for the treatment of Type 2 Diabetes in patients who are appropriate surgical candidates with BMI of 30 to 35 who are inadequately controlled by lifestyle and medical therapy." (Appendix 3 includes a detailed published summary of the Rome summit and a small selection of abstracts on the measurable reduction in Diabetes indicators following bariatric surgery.)

Based on the documented success from previous studies, CMS should consider coverage for those Medicare and Medicaid patients who would benefit from surgical intervention. Should CMS decide that a NCD is not warranted at this time, we urge CMS to permit local coverage discretion to continue, and would allow physicians the choice to treat Diabetic Patients surgically when deemed appropriate for that individual. Concurrently, clinical data on Medicare patients receiving these interventions will continue, important for evidence-based decision making.

We agree with the notion that additional studies will be important in determining which patients will receive the greatest benefit from surgical intervention. A national coverage decision that limits access would impede adoption of new promising techniques and could have the unintended consequences of severely restricting the ability to collect meaningful data on this patient population.

Conclusion

- We support the consideration of coverage for surgical intervention to treat selected patients with Type 2 Diabetes.
- We support the notion that ongoing and future studies may assist in determining the optimal course of therapy and could provide some further validation as to the group of patients most likely to benefit from surgical intervention
- It is evident from recent publications that there are patients who may substantially benefit from a surgical procedure that can put Type 2 Diabetes into remission, stop the progression of disease, and reduce the onset of devastating co-morbidities that are directly attributed to Diabetes.
- We respectfully request, should CMS conclude that a National Coverage Determination is not warranted at this time, that CMS allow the current process to continue through local discretion as additional studies provide additional supportive data.

Sincerely,

/signed/

Stuart A. Randle
President & CEO
GI Dynamics, Inc.
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Lexington, MA 02421

Michael Tarnoff MD FACS
Assistant Professor of Surgery
Minimally Invasive and Bariatric Surgery
Tufts Medical Center
Boston, MA

Appendix 1: About GI Dynamics and the EndoBarrier

GI Dynamics Corporate Summary
June 2008

Defining Noninvasive Metabolic Control

Background
With an estimated 70 million adults now obese in America, the Surgeon General and the health care community are awakening to the epidemic proportions of this disease and its socioeconomic implications. In the face of this growing crisis, attempts at medical weight loss with or without pharmacologic intervention have been found ineffective in the five million people annually seeking help. Bariatric surgery works well but due to its invasiveness and cost, surgeries are limited to 200,000 procedures performed annually. While the US has the lead in this epidemic, the world wide impact is now also being felt in numerous developing countries. The obesity problem cries out for a new, innovative approach to help patients deal with this disease. GI Dynamics is developing and commercializing revolutionary, noninvasive, removable devices that modify metabolic pathways to treat obesity and diabetes. In its animal and human clinical research, GI Dynamics has discovered that use of its devices has an immediate and profound effect on weight reduction as well as on reversing the clinical impact of type 2 diabetes.

Product Technology Concept
GI Dynamics has developed novel technologies for endoscopically-delivered and retrieved implants that directly effect metabolic pathways. Its EndoBarrier™ intestinal liner is an impermeable barrier that blocks food contact in the duodenum and proximal jejunum. This intestinal bypass mimics the effect of the Roux-en-Y gastric bypass surgery, producing similar weight loss and rapid resolution of type 2 diabetes.

The company is conducting several clinical trials which are showing that the EndoBarrier technology can produce excess weight-loss of 30% at 6 months in morbidly obese patients. It has also shown the potential for the rapid elimination of the need for medications to control glucose in diabetics.

Studies in animal models of both obesity and diabetes have begun to elucidate mechanisms of action that include a direct effect on glucose homeostasis as a result of duodenal exclusion and the delivery of undigested food to the proximal jejunum as well as delayed gastric emptying.

Current Status
EndoBarrier™ intestinal implants are in clinical trials globally and will begin a pivotal trial in the US next year. The target market is substantial – twenty million Americans are candidates for invasive bariatric surgery, and 60 million have BMI's between 30 and 40. These represent strong candidates for a safe, noninvasive alternative to surgery or drug therapy.

History
GI Dynamics was founded in 2003 based on the recognition of the emerging obesity problem and the invention of the Endobarrier™ patented technology. It has subsequently raised $46 million in three rounds of financing from top tier venture capital companies including Advanced Technology Ventures, Cutlass Capital, Domain Associates, Johnson & Johnson Development Corporation and Polaris Venture Partners. The company has also assembled a world class group of advisors with specialties in bariatric surgery, gastroenterology, endocrinology and medical weight loss.

Management
Stuart Randle, CEO
Andy Levine, CTO
Sherrie Coval-Goldsmith, VP Clinical and Regulatory
Jonathan Hartmann, VP Marketing
Robert Crane, CFO

Appendix 2: Rome Diabetes Surgical Summit and Selected Peer Reviewed Articles

JAMA. 2008 Jan 23;299(3):316-23.

Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial.

Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, Proietto J, Bailey M, Anderson M.

Centre for Obesity Research and Education, Monash University Medical School, The Alfred Hospital, Melbourne, Victoria, Australia. john.dixon@med.monash.edu.au

CONTEXT: Observational studies suggest that surgically induced loss of weight may be effective therapy for type 2 diabetes. OBJECTIVE: To determine if surgically induced weight loss results in better glycemic control and less need for diabetes medications than conventional approaches to weight loss and diabetes control. DESIGN, SETTING, AND PARTICIPANTS: Unblinded randomized controlled trial conducted from December 2002 through December 2006 at the University Obesity Research Center in Australia, with general community recruitment to established treatment programs. Participants were 60 obese patients (BMI >30 and <40) with recently diagnosed (<2 years) type 2 diabetes. INTERVENTIONS: Conventional diabetes therapy with a focus on weight loss by lifestyle change vs laparoscopic adjustable gastric banding with conventional diabetes care. MAIN OUTCOME MEASURES: Remission of type 2 diabetes (fasting glucose level <126 mg/dL [7.0 mmol/L] and glycated hemoglobin [HbA1c] value <6.2% while taking no glycemic therapy). Secondary measures included weight and components of the metabolic syndrome. Analysis was by intention-to-treat. RESULTS: Of the 60 patients enrolled, 55 (92%) completed the 2-year follow-up. Remission of type 2 diabetes was achieved by 22 (73%) in the surgical group and 4 (13%) in the conventional-therapy group. Relative risk of remission for the surgical group was 5.5 (95% confidence interval, 2.2-14.0). Surgical and conventional-therapy groups lost a mean (SD) of 20.7% (8.6%) and 1.7% (5.2%) of weight, respectively, at 2 years ($P < .001$). Remission of type 2 diabetes was related to weight loss ($R2 = 0.46$, $P < .001$) and lower baseline HbA1c levels (combined $R2 = 0.52$, $P < .001$). There were no serious complications in either group. CONCLUSIONS: Participants randomized to surgical therapy were more likely to achieve remission of type 2 diabetes through greater weight loss. These results need to be confirmed in a larger, more diverse population and have long-term efficacy assessed. TRIAL REGISTRATION: actr.org Identifier: ACTRN012605000159651.

Add to MyItinerary

Interim Report on a Prospective, Randomized Sham Controlled Trial Investigating a Completely Endoscopic Duodenal-Jejunal Bypass Sleeve for the Treatment of Type 2 Diabetes

Presented during:
Incretins

Year: 2008
Abstract Number: 103-OR

Authors:
MICHAEL TARNOFF, CHRISTOPHER SORLI, LEONARDO RODRIGUEZ, ALMINO RAMOS, MANOEL GALVAO, ELIANA REYES, PILAR FAGALDE, MARIA SOLEDAD OLTRA, JORGE SABA, MUNIR ALAMO, CARMEN GLORIA AYLWIN, CAROLINA PRIETO, *Boston, MA, Billings, MT, Santiago, Chile, Sao Paulo, Brazil*

Results:
Neurohormonal mechanisms (including incretins) as a result of duodenal bypass are increasingly implicated as important components of the rapid resolution of type 2 diabetes (T2DM) following gastric bypass surgery. This is the first report of a completely endoscopic 61 cm duodenal-jejunal bypass sleeve (DJBS) to specifically treat T2DM. In a single blind ongoing 52 week study, 18 T2DM patients were prospectively randomized to receive either the DJBS (n=12) or a sham endoscopy (n=6). Both groups were maintained on their baseline caloric intake for the first two weeks and are equally counseled about low calorie diet and healthy living at each subsequent visit. The primary endpoint is reduction of HbA1c from baseline at 12, 24 and 52 weeks. Select secondary endpoints include safety, fasting plasma glucose (FPG), 7-point glucose profile, total body weight loss (TBWL) and change in the area under the curve after meal tolerance testing (MTT AUC) as compared to baseline. One week data have been analyzed for all patients. At 1 week, the mean change in MTT AUC was -18.6% and +10.1% in device and sham groups respectively (p=0.05), FPG was -51.6 $\pm$43.5mg/dl and +16.5 $\pm$ 77.7mg/dl (p=0.17), and the aggregate reduction in 7 point glucose profile was -54.8 $\pm$ 54.5mg/dl and +1.1 $\pm$ 45.7mg/dl (p<0.05). Total body weight loss between groups was similar with -4.5 $\pm$ 1.3kg and -3.9 $\pm$ 1.3kg for device and sham, respectively (p>0.05). The 1 week results specifically highlight the ability of duodenal-jejunal bypass to rapidly restore glycemic control independent of weight loss or diet, implicating direct duodenal neurohormonal mechanisms. The durability of glycemic control with the DJBS requires further study, which is ongoing at this time.

Category:
01-E Clinical Therapeutics/New Technology - Treatment of Insulin Resistance

2007 Diabetes UK. Diabetic Medicine, 24, 1213–1220

Gastric bypass alters the dynamics and metabolic effects of insulin and proinsulin secretion

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Abstract

Aims Hyperproinsulinaemia is associated with obesity and is a risk factor for Type 2 diabetes. We explored the dynamics of proinsulin and insulin and postprandial effects on glucose and lipids in subjects who had undergone gastric bypass (GBP) surgery compared with morbidly obese (MO) subjects and normal weight control subjects (NW).

Methods Subjects free from diabetes were recruited: 10 previously MO subjects [body mass index (BMI) ± SD, 34.8 ± 6.2 kg/m^2] who had undergone GBP surgery, 10 MO subjects (BMI 44 ± 3.1 kg/m^2) and 12 NW control subjects (BMI 23.2 ± 2.4 kg/m^2). After an overnight fast, a standard meal (2400 kJ) was ingested and glucose, proinsulin, insulin free fatty acids and triglycerides were determined up to 180 min.

Results Fasting proinsulin was similar in the GBP group and NW control subjects, but threefold increased in MO subjects ($P < 0.05$). Postprandial AUC for glucose was similar in the three groups and AUC for proinsulin was high in MO, intermediate in the GBP group and lowest in NW control subjects (P for trend = 0.020). Postprandial proinsulin at 60 min was similar in the GBP group and MO subjects and twofold higher than in NW control subjects. Postprandial proinsulin at 180 min was normal in the GBP group, but fivefold increased in MO subjects ($P = 0.008$). Insulin increased rapidly at 30 min in the GBP group and was normal at 90 min, whereas insulin was still increased at 90–180 min in the MO subjects ($P < 0.001$).

Conclusions MO subjects, free from diabetes, have elevated proinsulin concentrations in the fasting as well as the postprandial phase. After GBP surgery markedly lower fasting and postprandial proinsulin concentrations were observed, although BMI was higher compared with NW control subjects.

Diabet. Med. 24, 1213–1220 (2007)

Keywords gastric by-pass, insulin, obesity, proinsulin

Abbreviations BMI, body mass index; CHD, coronary heart disease; FFA, free fatty acids; GBP, gastric bypass; IGT, impaired glucose tolerance; MO, morbid obesity; NW, normal weight; OGTT, oral glucose tolerance test; T2DM, Type 2 diabetes mellitus; TG, triglycerides

Annals of Surgery • Volume 243, Number 1, January 2006

Gut Hormone Profiles Following Bariatric Surgery Favor an Anorectic State, Facilitate Weight Loss, and Improve Metabolic Parameters

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Objective: To study the effect of bariatric surgery on the entero-hypothalamic endocrine axis of humans and rodents.

Background: Bariatric surgery is the most effective obesity treatment as it achieves substantial and sustained weight loss. Glycemic control and enhanced satiation improve before substantial weight loss occurs. Gut peptides, acting both peripherally and centrally, contribute to glycemic control and regulate food intake.

Methods: We examined meal-stimulated responses of insulin, ghrelin, peptide YY (PYY), glucagon-like-peptide-1 (GLP-1), and pancreatic polypeptide (PP) in humans and rodents following different bariatric surgical techniques.

Results: Compared with lean and obese controls, patients following Roux-en-Y gastric bypass (RYGB) had increased postprandial plasma PYY and GLP-1 favoring enhanced satiety. Furthermore, RYGB patients had early and exaggerated insulin responses, potentially mediating improved glycemic control. None of these effects were observed in patients losing equivalent weight through gastric banding. Leptin, ghrelin, and PP were similar in both the surgical groups. Using a rodent model of jejuno-intestinal bypass (JIB), we showed elevated PYY and GLP-1 in JIB rats compared with sham-operated rats. Moreover, exogenous PYY reduced food intake and blockade of endogenous PYY increased food intake. Thus, higher plasma PYY following JIB may contribute to reduced food intake and contribute to weight loss.

Conclusions: Following RYGB and JIB, a pleiotropic endocrine response may contribute to the improved glycemic control, appetite reduction, and long-term changes in body weight.

(*Ann Surg* 2006;243: 108–114)

Annals of Surgery • Volume 244, Number 5, November 2006

The Mechanism of Diabetes Control After Gastrointestinal Bypass Surgery Reveals a Role of the Proximal Small Intestine in the Pathophysiology of Type 2 Diabetes

Francesco Rubino, MD, Antonello Forgione, MD, David E. Cummings, MD, Michel Vix, MD, Donatella Gnuli, MD, Geltrude Mingrone, MD, Marco Castagneto, MD, and Jacques Marescaux, MD

Summary Background Data: Most patients who undergo Roux-en-Y gastric bypass (RYGB) experience rapid resolution of type 2 diabetes. Prior studies indicate that this results from more than gastric restriction and weight loss, implicating the rearranged intestine as a primary mediator. It is unclear, however, if diabetes improves because of enhanced delivery of nutrients to the distal intestine and increased secretion of hindgut signals that improve glucose homeostasis, or because of altered signals from the excluded segment of proximal intestine. We sought to distinguish between these two mechanisms.

Methods: Goto-Kakizaki (GK) type 2 diabetic rats underwent duodenal-jejunal bypass (DJB), a stomach-preserving RYGB that excludes the proximal intestine, or a gastrojejunostomy (GJ), which creates a shortcut for ingested nutrients without bypassing any intestine. Controls were pair-fed (PF) sham-operated and untreated GK rats. Rats that had undergone GJ were then reoperated to exclude the proximal intestine; and conversely, duodenal passage was restored in rats that had undergone DJB. Oral glucose tolerance (OGTT), food intake, body weight, and intestinal nutrient absorption were measured.

Results: There were no differences in food intake, body weight, or nutrient absorption among surgical groups. DJB-treated rats had markedly better oral glucose tolerance compared with all control groups as shown by lower peak and area-under-the-curve glucose values ($P < 0.001$ for both). GJ did not affect glucose homeostasis, but exclusion of duodenal nutrient passage in reoperated GJ rats significantly improved glucose tolerance. Conversely, restoration of duodenal passage in DJB rats reestablished impaired glucose tolerance.

Conclusions: This study shows that bypassing a short segment of proximal intestine directly ameliorates type 2 diabetes, independently of effects on food intake, body weight, malabsorption, or nutrient delivery to the hindgut. These findings suggest that a proximal intestinal bypass could be considered for diabetes treatment and that potentially undiscovered factors from the proximal bowel might contribute to the pathophysiology of type 2 diabetes.

(*Ann Surg* 2006;244: 741–749)

Diabetes Care, Volume 28, Number 11, November 2005

Laparoscopic Gastric Banding Prevents Type 2 Diabetes and Arterial Hypertension and Induces Their Remission in Morbid Obesity: A 4-year case-controlled study

Antonio E. Pontiroli, MD, Franco Folli, MD, PhD, Michele Paganelli, MD, Giancarlo Micheletto, MD, Pierluigi Pizzocri, MD, Paola Vedani, MD, Francesca Luisi, PhD, Lucia Perego, PhD, Alberto Morabito, PhD, Santo Bressani Doldi, MD

OBJECTIVE — Lifestyle modifications and pharmacological interventions can prevent type 2 diabetes in obese subjects with impaired glucose tolerance. The aim of this study was to compare laparoscopic adjustable gastric banding (LAGB) and conventional diet (No-LAGB) in the prevention (primary intervention study; 56 vs. 29 patients) and remission (secondary intervention study; 17 vs. 20 patients) of type 2 diabetes and hypertension in grade 3 obesity in a 4-year study.

RESEARCH DESIGN AND METHODS — The subjects (n = 122; age 48.5 ± 1.05 years; BMI 45.7 ± 0.67 kg/m^2) underwent a diagnostic workup, including psychological and psychiatric assessments, in preparation for the LAGB procedure. Of the 122 subjects, 73 had the surgery (LAGB group). The control group (No-LAGB group) consisted of the 49 subjects who refused the surgery but agreed to be followed up; 6 of these subjects dropped out by the 2nd year of the study, so that the final number of patients was 73 and 43 in the LAGB and No-LAGB groups, respectively. All patients had a yearly visit and oral glucose tolerance test.

RESULTS — From baseline to the end of the 4-year follow-up, BMI decreased from 45.9 ± 0.89 at baseline to 37.7 ± 0.71 kg/m^2 in the LAGB group and remained steady in the No-LAGB group (from 45.2 ± 1.04 to 46.5 ± 1.37 kg/m^2), with no significant differences between the primary and secondary intervention groups. In the primary intervention study, five of the No-LAGB subjects (17.2%) and none of the LAGB subjects (0.0%; P = 0.0001) progressed to type 2 diabetes; in the secondary intervention study, type 2 diabetes remitted in one No-LAGB patient (4.0%) and seven LAGB patients (45.0%; P = 0.0052). Hypertension occurred in 11 No-LAGB patients (25.6%) and 1 LAGB patient (1.4%; P = 0.0001) and remitted in 1 No-LAGB (2.3%) and 15 LAGB patients (20.5%; P = 0.0001). A study of body mass composition revealed a significant reduction of fat mass and a transitory, but not significant, decrease of fat-free mass in LAGB patients.

CONCLUSIONS — In morbid obesity, sustained and long-lasting weight loss obtained through LAGB prevents the occurrence of type 2 diabetes and hypertension and decreases the prevalence of these disorders.

Diabetes Care 28:2703–2709, 2005

Annals of Surgery • Volume 240, Number 2, August 2004

Effects of Bariatric Surgery in Older Patients

Harvey J. Sugerman, MD, Eric J. DeMaria, MD, John M. Kellum, MD, Elizabeth L. Sugerman, BSN, Jill G. Meador, BSN, and Luke G. Wolfe, MS

Objective: Evaluate the safety and efficacy of bariatric surgery in older patients.

Background: Because of an increased morbidity in older patients who may not be as active as younger individuals, there remain concerns that they may not tolerate the operation well or lose adequate amounts of weight.

Methods: The database of patients who had undergone bariatric surgery since 1980 and National Death Index were queried for patients <60 and ≥ 60 years of age. GBP was the procedure of choice after 1985. Data evaluated at 1 and 5 years included weight lost, % weight lost (%WL), % excess weight loss (%EWL), % ideal body weight (%IBW), mortality, complications, and obesity comorbidity.

Results: Eighty patients underwent bariatric surgery: age 63 ± 3 years, 78% women, 68 white, 132 ± 22 kg, BMI 49 ± 7 kg/m^2, 217 ± 32%IBW. Preoperative comorbidity, was greater ($P < 0.001$) in patients ≥ 60 years. There were no operative deaths but 11 late deaths. Complications: 4 major wound infections, 2 anastomotic leaks, 10 symptomatic marginal ulcers, 5 stomal stenoses, 3 bowel obstructions, 26 incisional hernias (nonlaparoscopic), and 1 pulmonary embolism. At 1 year after surgery (94% follow-up), patients lost 38 ± 11 kg, 57%EWL, 30%WL, BMI 34.5 ± 7 kg/m^2, %IBW 153 ± 31. Comorbidities decreased ($P < 0.001$); however, %WL and %EWL and improvement in hypertension and orthopedic problems, although significant, were greater in younger patients. At 5 years after surgery (58% follow-up), they had lost 31 ± 18 kg, 50%EWL, 26%WL, BMI 35 ± 8 kg/m^2, and %IBW 156 ± 36.

Conclusions: Bariatric surgery was effective for older patients with a low morbidity and mortality. Older patients had more pre- and post-operative comorbidities and lost less weight than younger patients. However the weight loss and improvement in comorbidities in older patients were clinically significant.

(*Ann Surg* 2004;240: 243–247)

Annals Of Surgery, Vol. 237, No. 6, 751–758, 2003

Harvey J. Sugerman, MD, Luke G. Wolfe, MS, Domenic A. Sica, MD, and John N. Clore, MD

Diabetes and Hypertension in Severe Obesity and Effects of Gastric Bypass-Induced Weight Loss

Objective

To evaluate the preoperative relationships of hypertension and diabetes mellitus in severe obesity and the effects of gastric bypass (GBP)-induced weight loss.

Summary Background Data

Severe obesity is associated with multiple comorbidities, particularly hypertension and type 2 diabetes mellitus, that may affect life expectancy.

Methods

The database of patients who had undergone GBP by one general surgeon at a university hospital between September 1981 and January 2000 was queried as to weight, body mass index (BMI), pre- and postoperative diabetes, hypertension, and other comorbidities, including sleep apnea, hypoventilation, gastroesophageal reflux, degenerative joint disease, urinary incontinence, venous stasis, and pseudotumor cerebri.

Results

Of 1,025 patients treated, 15% had type 2 diabetes mellitus and 51% had hypertension. Of those with diabetes, 75% also had hypertension. There was a progressive increase in age between patients who had neither diabetes nor hypertension, either diabetes or hypertension, or both diabetes and hypertension. At 1 year after GBP (91% follow-up), patients lost 66 ± 18% excess weight (%EWL) or 35 ± 9% of their initial weight (%WL). Hypertension resolved in 69% and diabetes in 83%. Patients who resolved their hypertension or diabetes had greater %EWL and %WL than those who did not. African-American patients had a higher risk of hypertension than whites before GBP and were less likely to correct their hypertension after GBP. There was significant resolution of other obesity comorbidity problems. At 5 to 7 years after GBP (50% follow-up), %EWL was 59 ± 24 and %WL was 31 ± 13; resolution of hypertension was 66% and diabetes 86%.

Conclusions

These data suggest that type 2 diabetes mellitus and hypertension may be indirectly related to each other through the effects of obesity, but not directly as to cause and effect. The longer a person remains severely obese, the more likely he or she is to develop diabetes, hypertension, or both. GBP-induced weight loss is effective in correcting diabetes, hypertension, and other comorbidities but is related to the %EWL achieved. Severely obese African-Americans were more likely to have hypertension and respond less well to GBP surgery than whites. These data suggest that GBP surgery for severe obesity should be provided earlier to patients to prevent the development of diabetes and hypertension and their complications.

Annals of Surgery • Volume 238, Number 4, October 2003

Effect of Laparoscopic Roux-En Y Gastric Bypass on Type 2 Diabetes Mellitus

Philip R. Schauer, MD, Bartolome Burguera, MD, Sayeed Ikramuddin, MD, Dan Cottam, MD, William Gourash, CRNP, Giselle Hamad, MD, George M. Eid, MD, Samer Mattar, MD, Ramesh Ramanathan, MD, Emma Barinas-Mitchel, PhD, R. Harsha Rao, MD, Lewis Kuller, MD DrPH, and David Kelley, MD

Objective: To evaluate pre- and postoperative clinical parameters associated with improvement of diabetes up to 4 years after laparoscopic Roux-en-Y gastric bypass (LRYGBP) in patients with type 2 diabetes mellitus (T2DM).

Summary Background Data: The surgical treatment of morbid obesity leads to dramatic improvement in the comorbidity status of most patients with T2DM. However, little is known concerning what preoperative clinical factors are associated with postoperative long-term improvement in diabetes in the morbidly obese patient with diabetes.

Methods: We evaluated pre- and postoperative data, including demographics, duration of diabetes, metabolic parameters, and clinical outcomes, in all patients with impaired fasting glucose (IFG) and type T2DM undergoing LRYGBP from July 1997 to May 2002.

Results: During this 5-year period, 1160 patients underwent LRYGBP and 240 (21%) had IFG or T2DM. Follow up was possible in 191 of 240 patients (80%). There were 144 females (75%) with a mean preoperative age of 48 years (range, 26–67 years). After surgery, weight and body mass index decreased from 308 lbs and 50.1 kg/m^2 to 211 lbs and 34 kg/m^2 for a mean weight loss of 97 lbs and mean excess weight loss of 60%. Fasting plasma glucose and glycosylated hemoglobin concentrations returned to normal levels (83%) or markedly improved (17%) in all patients. A significant reduction in use of oral antidiabetic agents (80%) and insulin (79%) followed surgical treatment. Patients with the shortest duration (<5 years), the mildest form of T2DM (diet controlled), and the greatest weight loss after surgery were most likely to achieve complete resolution of T2DM.

Conclusion: LRYGBP resulted in significant weight loss (60% percent of excess body weight loss) and resolution (83%) of T2DM. Patients with the shortest duration and mildest form of T2DM had a higher rate of T2DM resolution after surgery, suggesting that early surgical intervention is warranted to increase the likelihood of rendering patients euglycemic.

(*Ann Surg* 2003;238: 467–485)

N Engl J Med 2003;348:383-93

Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes

Peter Gæde, M.D., Pernille Vedel, M.D., Ph.D., Nicolai Larsen, M.D., Ph.D., Gunnar V.H. Jensen, M.D., Ph.D., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.

BACKGROUND

Cardiovascular morbidity is a major burden in patients with type 2 diabetes. In the Steno-2 Study, we compared the effect of a targeted, intensified, multifactorial intervention with that of conventional treatment on modifiable risk factors for cardiovascular disease in patients with type 2 diabetes and microalbuminuria.

METHODS

The primary end point of this open, parallel trial was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization, and amputation. Eighty patients were randomly assigned to receive conventional treatment in accordance with national guidelines and 80 to receive intensive treatment, with a stepwise implementation of behavior modification and pharmacologic therapy that targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, along with secondary prevention of cardiovascular disease with aspirin.

RESULTS

The mean age of the patients was 55.1 years, and the mean follow-up was 7.8 years. The decline in glycosylated hemoglobin values, systolic and diastolic blood pressure, serum cholesterol and triglyceride levels measured after an overnight fast, and urinary albumin excretion rate were all significantly greater in the intensive-therapy group than in the conventional-therapy group. Patients receiving intensive therapy also had a significantly lower risk of cardiovascular disease (hazard ratio, 0.47; 95 percent confidence interval, 0.24 to 0.73), nephropathy (hazard ratio, 0.39; 95 percent confidence interval, 0.17 to 0.87), retinopathy (hazard ratio, 0.42; 95 percent confidence interval, 0.21 to 0.86), and autonomic neuropathy (hazard ratio, 0.37; 95 percent confidence interval, 0.18 to 0.79).

CONCLUSIONS

A target-driven, long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria reduces the risk of cardiovascular and microvascular events by about 50 percent.

Annals Of Surgery, Vol. 227, No. 5, 637-644, 1998

A New Paradigm for Type 2 Diabetes Mellitus: Could It Be a Disease of the Foregut?

Matthew S. Hickey, PhD, Walter J. Pories, MD, Kenneth G. MacDonald, Jr., MD, Kelly A. Cory, PhD,t G. Lynis Dohm, PhD, Melvin S. Swanson, PhD, Richard G. Israel, PhD, Hisham A. Barakat, PhD, Robert V. Considine, PhD, Jose F. Caro, MD, and Joseph A. Houmard, PhD

Summary Background Data

We previously reported, in a study of 608 patients, that the gastric bypass operation (GB) controls type 2 diabetes mellitus in the morbidly obese patient more effectively than any medical therapy. Further, we showed for the first time that it was possible to reduce the mortality from diabetes; GB reduced the chance of dying from 4.5% per year to 1% per year. This control of diabetes has been ascribed to the weight loss induced by the operation. These studies, in weight-stable women, were designed to determine whether weight loss was really the important factor.

Methods

Fasting plasma insulin, fasting plasma glucose, minimal model-derived insulin sensitivity and leptin levels were measured in carefully matched cohorts: six women who had undergone GB and had been stable at their lowered weight 24 to 30 months after surgery *versus* a control group of six women who did not undergo surgery and were similarly weight-stable. The two groups were matched in age, percentage of fat, body mass index, waist circumference, and aerobic capacity.

Results

Even though the two groups of patients were closely matched in weight, age, percentage of fat, and even aerobic capacity, and with both groups maintaining stable weights, the surgical group demonstrated significantly lower levels of serum leptin, fasting plasma insulin, and fasting plasma glucose compared to the control group. Similarly, minimal model-derived insulin sensitivity was significantly higher in the surgical group. Finally, self-reported food intake was significantly lower in the surgical group.

Conclusions

Weight loss is not the reason why GB controls diabetes mellitus. Instead, bypassing the foregut and reducing food intake produce the profound long-term alterations in glucose metabolism and insulin action. These findings suggest that our current paradigms of type 2 diabetes mellitus deserve review. The critical lesion may lie in abnormal signals from the gut.

Special Report: Rome Diabetes Surgery Summit

March 29-31, 2007

by Eric Klein, CEO, ObesityHelp, Inc.

Bariatrics Today is pleased to bring you comprehensive coverage of the Diabetes Surgery Summit (DSS), which took place on March 28-31, 2007, in Rome, Italy. In these pages we bring you a summary of the proceedings, including voting data and comments from some of the key participants.

IN THIS SECTION

The Seeds of Consensus

A consensus statement has not yet been issued, but when it is released it might contain language similar to the following:

"Gastrointestinal surgery may be appropriate for the treatment of type 2 diabetes in patients who are appropriate surgical candidates with BMI of 30 to 35 who are inadequately controlled by lifestyle and medical therapy."

Percentage of voting members agreeing with this statement: 82% (interim partial result)

Extent of agreement on a per-surgery basis:

LAGB	66% (interim partial result)
RYGB	73% (interim partial result)
BPD/DS	33% (interim partial result)
Gastric Sleeve	24% (interim partial result)

DSS in Brief

Approximately 150 medical professionals and other concerned individuals, 49 of whom were voting panelists, met under the leadership of doctors Francesco Rubino, David Cummings, Lee Kaplan and Phillip Schauer to seek expert consensus on the use of gastrointestinal surgery as a treatment for type 2 diabetes. This was the first official Diabetes Surgery Seminar (www.dssrome2007.com). Only 37 percent of the voting panelists were surgeons, a significant fact—and 57 percent of the voting panelists were from the United States. The organizing committee has yet to compile a single statement of recommendation at the time of print, but the committee will draw upon collective recommendations made public at the conference by the voting panelists who voted on many independent statements. Key to this discussion was how to address the very large diabetic population within the BMI of 30 to 35 range. Eighty-two percent of the voting panelists agreed that gastrointestinal surgery "may be appropriate" for this group, under the conditions that (a) such individuals are suitable for surgery in general and (b) that their diabetes was not adequately controlled by lifestyle and medical therapy. The next step involves packaging a formal recommendation, sending it to voting panelists, and then sending it to endorsing organizations for consideration.

DSS—Early Reactions

Mike Tarnoff, MD FACS
Tufts New England Medical Center

The most exciting take home message from my perspective is that for the first time, a multidisciplinary panel of experts agreed, amongst other things, on the following:

1. Bariatric surgery, and in particular gastric bypass, possesses characteristics that likely enhance glucose tolerance by a mechanism that is independent of weight loss and with results that are likely superior to conventional medical therapy. While there was considerable debate about the quality of literature in support of this, the repetitive nature of the findings across the bariatric surgery literature in this regard caught the attention of the endocrinologists and highlighted the need for more targeted physician and patient education about the benefits of bariatric surgery as an independent T2DM treatment in the morbidly obese population.

2. The conclusion that bariatric surgery could serve as a therapeutic option for T2DM in the BMI 30-35 population is quite significant and lends support to a mounting campaign that the BMI criterion established in 1991 should be revised downward given the overwhelming efficacy and increasing safety of bariatric surgery.

3. Novel surgical options that preserve the integrity of the stomach should be studied under the close scrutiny of IRB and/or other relevant overweight committees. These options will be important for the significant numbers of T2DM patients whose BMI is below 30 and therefore don't need or want the gastric "restrictive" aspects of current bariatric surgery.

I found these points to be the most significant and the most likely to result in a necessary change in the standard of care.

David Cummings, MD
Assistant Professor of Medicine, Division of Metabolism, Endocrinology and Nutrition, University of Washington

Dr. Cummings noted that there is overwhelming evidence indicating that several types of bariatric operations promote profound weight loss and cause complete remission of type 2 diabetes. Most interestingly, these beneficial effects on diabetes are commonly observed within days after surgery, and they appear to be caused by mechanisms extending beyond just the consequences of weight loss, most likely involving changes in gastrointestinal hormones.

Examples of these hormonal changes include the following:
1. enhanced secretion of the GLP-1 due to surgical shortcuts for ingested nutrients to reach the lower intestine;
2. removal of the upper small intestine from contact with food;
3. lowering levels of the stomach hormone ghrelin.
Dr. Cummings also stated that continued research should increasingly enable the pharmacological manipulation of these natural systems regulating appetite and blood sugar, so that we can achieve at least some of the impressive effects of bariatric surgery with medications.

Kelvin D. Higa, MD, FACS
Assistant Clinical Professor in Surgery
University of California, San Francisco—Fresno
President Elect, ASBS

Personally, I was intrigued by the almost universal agreement among the non-surgeons that bariatric surgery was a viable option for the morbidly obese individuals (BMI > 40) with type II diabetes despite lack of recognition of bariatric surgery in previous published guidelines. I think the non-surgeons were interested in the early surgical data for lesser obese patients, and although one might think it a conflict of interest advocating surgical over medical treatment, the irony is the potential for study in the surgical population that can lead to a better understanding of the complex nature of incretins and other mechanisms that may ultimately replace surgical procedures in the treatment of not only obesity, but of better diabetic management. It was also interesting that non-surgeons strive for "control" of type II diabetes, but surgeons prefer the concept of "remission".

Lee M. Kaplan, MD, PhD
Director, MGH Weight Center, Massachusetts General Hospital and Harvard Medical School

Several lines of evidence in humans and animal models suggest that gastrointestinal weight loss surgery can have a dramatic, long-lasting, beneficial effect on type 2 diabetes. What is less clear is the risk/benefit relationship and appropriate use of surgery to treat diabetes in different groups of patients. We need to make research in this area a priority in order to determine the patients who would most benefit from this approach and the types of surgery that would be optimal. The Diabetes Surgery Summit was convened to review the current state of our knowledge, assess which patients with diabetes would likely benefit from surgical therapy, and develop guidelines for further research. It included clinicians and scientists from 25 countries in diverse medical and surgical specialties. Despite its diversity and wide variation in clinical practice, the faculty achieved strong consensus in several areas. As a result, we are hopeful that the recommendations coming from this meeting will strongly facilitate progress in understanding and exploiting the role of the gastrointestinal tract in regulating metabolism and controlling type 2 diabetes.

Why DSS Matters—Review and Commentary

Like many others, I attended the Diabetes Surgery Summit as an observer with some passion for the topic from a patient-care perspective. As the founder of ObesityHelp.com, I've been disturbed, year after year, to follow the plight of medicated diabetic patients joining the Website with BMI's below 40 or 35. Many of these patients had manageable symptoms which, rather than being resolved through appropriate and targeted treatment, generally got worse over time unless they had surgery. Typically, it was only a matter of years before they gained enough weight to qualify for surgery, but in the meantime they remained at risk for life-threatening diabetic consequences, particularly if they were concerned enough about their weight to keep themselves in that sub-35 "go nowhere zone." Many of us in the field have had the unfortunate experience of seeing surgical candidates (or near-candidates) actually die from diabetes while waiting for approval.

The memory of one such ObesityHelp (OH) member that I met in 1999 will always be with me. "Joe," as I will call him here, suffered from type 2 diabetes, and he believed until his dying day—not long after I met him—that his condition was somehow his fault. But the diabetes wasn't his problem from the perspective of society at large, and, sadly, even the medical professionals handling his case. His crime was that he was fat. His BMI was about 37, but Joe was deemed not heavy enough to warrant life-saving surgery. His health plan denied coverage for surgery and none of his other health care providers seemed particularly motivated to appeal this decision, because—in their own words to him—they saw it as an easy way out. They left Joe feeling unsupported and guilty. Joe's obesity robbed his diabetes of clinical attention, his obesity depriving his diabetes of autonomous status as a disease state and reducing it to the level of a mere co-morbidity of obesity. That, in turn, lead directly and singularly to the empty exhortation of "you need to eat less." Joe's interest in bariatric surgery was, in their minds, a testament to his being an uncommitted or even uncooperative patient, and in the rushed 10 minute HMO setting, every ounce of attention tied up in that focus was time away from focusing on managing his medication or his vascular problems. The reason this case stands out in my mind is because for the first weeks that I knew Joe, I didn't even know he was overweight; unlike most of his peers, he almost never even men-

tioned his weight. The only thing I heard Joe talking about was his diabetes, which he knew would kill him if it wasn't treated. It wasn't, and it did. Yes, he was concerned about his weight, but he had already lost some digits and some of his sight and it was those things which motivated him to take better care of himself, even as metabolic studies showed he burned an amazingly low 800 calories per day. He died, feeling that is predicament was his fault. He wanted to be seen as a diabetic patient and he wanted surgery to cure that diabetes (he was up on the literature, which was very convincing even back then), but the health care system didn't take his diabetes focus seriously and instead kept him in a fatal obesity cul-de-sac. Over the years, I've seen literally hundreds just like him cry out for help. I knew that the day for people like Joe would come, and that the DSS conference was likely part of that day.

Also, I had a strong interest in seeing what was really behind a consensus meeting that, on the surface, first seem to be driven by bariatric surgeons from the US. The fact that the American Diabetes Association (ADA) had joined with somewhat lesser known non-surgical organizations to endorse the topic certainly caught my attention, because the ADA's conferences, in particular, have historically given very little attention to bariatric surgery, and what attention was paid seemed to focus on clinical risks. It became clear that the endorsing organizations were endorsing the discussion and were under no obligation to go along with any summary recommendations from the organizing body. I was also intrigued by the consensus process. I wanted to learn the mechanics behind these proclamations—so rare, yet so lasting—that define the way policy is shaped and insurance letters are written for years to come. In my view, anything that would increase awareness amongst a wider range of care providers could only bode well for patients, many of whom are OH members.

The Road to Rome

According to the organizing committee, diabetes—a disease not presently curable by medicine—currently impacts more than 240 million people worldwide. This number is expected to surpass 380 million by 2025. About 93 percent of the people affected have type 2 diabetes. These numbers constitute an epidemic poised to completely overrun the world's healthcare systems unless something is done to stem the tide. While pharmacological developments in diabetes have been proceeding at a steady pace,

Steps in the Consensus Process

The steps below, outlining the process for the emergence of a consensus statement, might remind some American readers of the popular 1970's "Schoolhouse Rocks" cartoon, "How a Bill Becomes a Law." Steps in bold represent significant potential milestones towards generalized adoption in practice.

1. A panel of voting members is carefully selected to represent breadth of perspective. Since the focus of the discussion was surgery, the panel was organized to include a 60% majority of non-surgeons to ensure a diversity and balance of perspective.

2. The discussion process is endorsed by major organizations. These organizations endorse the idea of having a meeting to discuss the topic but are under no obligation to subsequently endorse any recommendations the group makes.

3. These people, along with about 100 non-voting peers, meet for three days.

4. Two days of presentation of recent scientific findings.

5. One day of voting. 49 of the invited 50 individuals were present for voting. In response to statements presented on a screen, each used a hand-held remote control voting machine to vote either "Yes", "No", or "Abstain". Their collective results are displayed on the screen after a minute allotted for voting.

6. The language of multiple statements is altered, section by section, with each new phrasing receiving a different percentage of "Yes" votes.

7. Anything higher than 2/3 is considered "a consensus", with many statements scoring in the 70s, 80s or 90s. Most were in the 90's or 100.

8. Semantic and other considerations are worked through to come up with a set of consensus summary positions.

9. The conference concludes.

10. The organizing committee forms a standing working group to continue progress.

11. The organizing committee draws upon the summary positions from the conference in order to prepare a consensual summary statement.

12. That statement is presented again to the voting panel members.

13. The resulting statement is then presented to the various organizations who endorsed the discussion.

14. Each organization indicates whether or not it supports the summary statement.

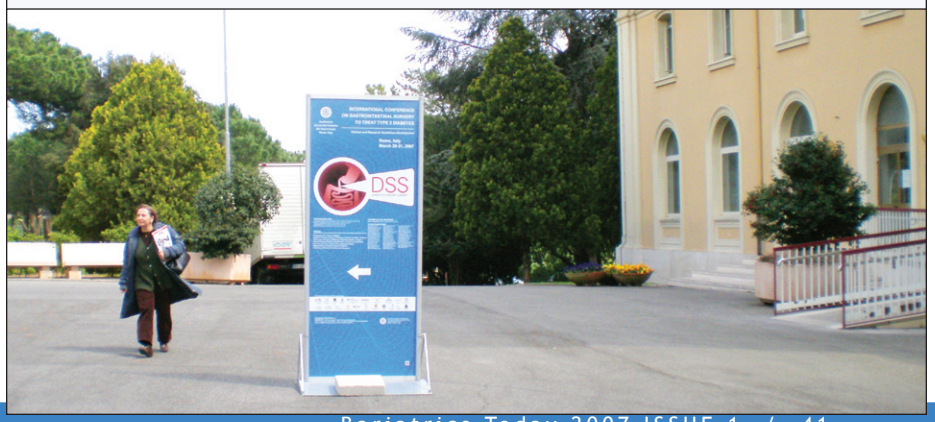
15. Organizations are free to provide specific input into ongoing and future dialogue.

16. The consensus statement is published.

17. The cycle may continue or repeat in the future.

18. At some point, various government regulatory organizations might come to endorse or adopt the consensus statement, especially if it has the backing of all or most relevant clinical academic organizations.

19. Down the road, and not part of the DSS consensus process, various government and private providers of insurance may follow suit and hold their own meetings to decide to reimburse or cover treatment in ways consistent with the DSS consensus.



Defining the Terms of Consensus

Here are four examples of concepts that were added or refined during the conversation.

"Gastrointestinal metabolic surgery"

This term was replaced with Gastrointestinal (GI) surgery. The motion of "metabolic surgery" was clearly recognized as a well intended effort to promote a concept, but use of the term "metabolic" was nevertheless ultimately more confusing than it was worth, even though many thought the term gastrointestinal was either too vague or too limiting. A dialogue between Dr.'s Buchwald and Dr. Schauer illustrated this when Dr. Buchwald suggested that the term be left open to future developments. He cited how the 1991 consensus technically only mentioned VBG and RNY, saying nothing about other developments, with the implication that, technically, anyone performing bariatric surgeries other than the VBG and the RNY were not within NIH guidelines. Dr. Schauer responded something to the effect that the consensus represents the opportunity to make particular recommendations based on particular knowledge available at the time of the consensus, and that ideally, the NIH consensus should have been revised after, say, five years.

"Severe Obesity"

This was originally used for some time in the discussion (serving implicitly as the modern revised term replacing "morbid obesity") but at one point was dropped in favor of explicitly stating BMI values.

"Appropriate suitable candidates"

This was added to validate the reality that for certain patients major surgery of any type is out of the question.

"Inadequately controlled by lifestyle and medical therapy"

It was decided not to elaborate what this meant at this present juncture. It was pointed out that control was different from severity. For example, patients may be in worse case if their Hb1Ac levels are comparatively low but which have gone untreated for a long time, potentially opening up the door for debate on disease state terminology.

even more noteworthy is the highly predictable way in which weight loss surgery (WLS) almost always leads to at least some improvement (sometimes major) in patients with type 2 diabetes. That WLS can have such a therapeutic effect on diabetes has three major ramifications. It suggests that:

1. Bariatric surgery is a procedure that increases quality of life and presumed life span, rather than serving merely a cosmetic purpose.
2. It might actually make sense to consider, in some cases at least, using surgery explicitly to treat diabetes.
3. Surgical treatment of diabetes may be a rich source of information about the physiological basis of diabetes.

While the first of these ramifications is nothing new to the bariatric and medical communities, the second—that diabetes may be treated surgically as an end in itself—represents a profound disruption to current paradigms amongst non-surgeons. It also raises the possibility of a major shift in the balance of power and economic fortune toward the surgical profession, with all other professionals becoming relatively less important, possibly spelling less funding (academic) and reimbursement (private) for non-surgical intervention.

Some claim that the surgical device industry would love to push the allowed BMI down to 25 for surgical intervention—generating a potential market of 100 million people in the United States alone (envision outpatient surgical centers on every street corner)—while others argue that non-surgeons, backed by pharmaceutical companies, already have enjoyed this scenario for decades (a doctor's office, well-stocked with pharmaceutical samples, on every corner). More significantly, some would claim the non-surgeons are working against the patient's best interest by using their majority status within governing medical regulatory bodies to delay the spread of life-saving innovative technology. Whether or not the relative shift in social and economic status towards surgical teams becomes definitive or far reaching, the sheer demographic reality at hand will place significant demands upon all professional and business spheres. One DSS conference participant expressed this point with some eloquence: "Either you find some way to effectively treat the diabetes now or the number of morbidly obese individuals is going to soon become so great that all the surgeons in the country doing bariatric surgery full time wouldn't be enough to put a dent in it."

The fact is that weight loss surgery patients experience a reduction in or resolution of diabetic symptoms immediately following surgery, before weight loss has had a chance to take place, indicating that the mechanism is a disruption of endocrine/paracrine feedback mechanisms rooted within the gut. As the third ramification implies, a better understanding of the histological changes caused by the various types of gastric surgery should shed additional light on the physiology of insulin regulation and resistance, as mediated by several known and suspected factors found within the intraluminal tissues.

Consensus is Not Built in a Day

Two days of presentation provided a very high quality summary from all the relevant fields. Some of the newer information included results on sleeve gastrectomy, enterectomy, omentectomy and intraluminal duodenal sleeves. Physiology discussion covered incretins and differential roles of the foregut and hindgut.

Diabetes is a disorder of physiology rooted in organ-specific histology. Traditionally most clinicians have viewed insulin resistance as a type of endocrinological dialogue primarily between the active beta cells of the pancreas and more or less uniformly passive peripheral cells that more or less just sit there developing insulin resistance because the pancreas makes too much of it in response to food. From this standpoint there is something inherently mysterious—and in need of comprehensive explanation—about how changing the intestine would have anything to do with diabetes. The conference presentations made it clear, however, that gut tissue plays an active regulatory role. From this standpoint, the mystery is removed. It makes no less sense to wonder why removing gut tissue would disrupt diabetes than it would to wonder why removing pancreas tissue would disrupt diabetes even if the particular interrelated endocrine pathways have yet to be completely mapped out and understood.

Once one accepts that paradigm on a fundamental level, then the topic in a way becomes very matter-of-fact. One can see using surgery as merely yet another tool, along with medication, as a way to treat a

metabolic disorder. If research has yet to demonstrate conclusively exactly how surgery impacts diabetes, then that merely puts surgery in the same boat as many medications. Drugs are often discovered to be safe and effective many years before their mechanism is understood.

From the data it was pretty clear that studies have been creeping into the lower BMI range, implying a worldwide de-facto shift in practice patterns, especially outside the United States. The general disorganization of the data for the most part gave one the strong impression that there was little worldwide coordinated guidance for research or clinical trials.

What stood out in my mind more than that, however, was the overwhelming amount of data that was available. Diabetes resolution and bariatric surgery had been big news, in a sense, for quite a while. In my case, I remember first hearing lengthy academic discussion on the topic back at the IFSO meeting in Crete in 2001. Plenty of data was extant, but it just hasn't been in the right form. Many weight loss surgery studies have been limited to BMIs of 30-35 on the low end and 50+ on the high end, with the 35-50 range being the primary lump on the subject weight histograph.

If one were to add up all the little 30-35 BMI piles across all these studies, then there are many hundreds of solid individual cases. I was pleased to learn of a meta-analysis which had done just that, but I gained a newfound respect for the challenge of doing this. The various experimental conditions from study to study simply vary too much. What one wants to see are results to compare from several studies where the association between surgical intervention and diabetes in the 30-35 range was the primary hypothesis being tested, rather than this being just an aside. That's what was missing, which is very frustrating. As I saw the data being presented, most of it a continuation of what we see at ASBS

Anatomy of Resolution—It's All in the Words

Because this topic has such potentially far-sweeping consequences, this section is being included to educate the reader about the process behind consensus. While the actual information here is, to the best of the author's knowledge, true, it represents merely an overview of some of the important steps covered over the course of several hours of voting. Some readers might find this to be an interesting process.

While this information is public domain, with many observers of several types having been present, the reader should note that these steps are tools to a committee whose work is still in process. The organizing committee is using the information below to formulate an official statement. The steps below reflect information that the committee has available to it as it formulates that position statement, which will likely contain several components.

First, the process began with a reality-check:

Collaboration among endocrinologists, surgeons and basic investigators should be encouraged to facilitate the understanding of GI mechanisms of metabolic regulation and to allow use of these mechanisms for improved treatment of type 2 diabetes. [Was put up for vote]

That statement received unanimous approval. Then, a basic template was presented to start off conversation. This template was informed by data presented during the previous two days. Note that it contained multiple sections each open for discussion and voting. Technically, a statement with 4 parts each with 4 possibilities generates over 100 different permutations to cover. Instead of covering all of these cases—which would take weeks and could turn even the most inspired brains to complete mush—the process involved the moderators leading discussion through a specific path through N-dimensional space. This is the only feasible method. Technically, this method does carry some subjective bias—ultimately a necessary product of humans being involved—in the sense that the conversation carried a particular mindset momentum at each stage of the process. Taking one route versus another (i.e., dealing with different variables in different orders) could theoretically lead to different final outcomes.

Starting Template:
Gastrointestinal metabolic surgery (which to include? LAGB, RYGB, BPD) appears to be a promising approach (which to use? a reasonable option / appropriate / indicated / recommended) to/for the treatment of inadequately controlled type 2 diabetes (HbA1c > 8.0 / 7.5 / 7.0) in patients with (severe?) obesity with a BM I≥ (which to use? 45/40/35/30).

From this point on, particular phrases were voted on, with each statement being presented with the percentage of voters voting "Yes" to the statement. Below were some of them. Note how "metabolic surgery" was replaced with "GI surgery." This was after much discussion. The following statements received varying degrees of high approval, inversely proportional to the strength of the wording:

GI metabolic surgery appears to be a promising approach for the treatment of type 2 diabetes inadequately controlled by lifestyle and medical therapy in patients with BMI ≥ 35. [Was put up for vote]

GI surgery is indicated for the treatment of type 2 diabetes inadequately controlled by lifestyle and medical therapy in patients with a BMI ≥ 35. [Was put up for vote]

GI surgery is recommended for the treatment of type 2 diabetes in appropriately selected patients with BMI ≥ 35 inadequately controlled by lifestyle and medical therapy. [Was put up for vote]

GI surgery should be considered for the treatment of type 2 diabetes in appropriately selected patients with BMI ≥ 35 inadequately controlled by lifestyle and medical therapy. [Was put up for vote]

At this juncture, before moving downward with a lower BMI, two elaborating branching points were considered. First, what defines "adequate control"? Discussion on this was postponed for later.

GI surgery is recommended for the treatment of type 2 diabetes in patients who are appropriate surgical candidates with BMI > 35. [Was put up for vote; failed to achieve majorly]

GI surgery should be considered for the treatment of type 2 diabetes in patients who are appropriate surgical candidates with BMI > 35. [Was put up for vote]

GI surgery should be considered for the treatment of type 2 diabetes in patients who are appropriate surgical candidates with BMI ≥ 35 who are inadequately controlled by lifestyle and medical therapy. [Was put up for vote]

GI surgery should be considered for the treatment of type 2 diabetes in patients who are appropriate surgical candidates with BMI ≥ 35 who are inadequately controlled by lifestyle and medical therapy. [Was put up for vote; received unanimous approval]

At this point it was observed (cynically by some) that the 1991 consensus had at last been validated. The next step was to move into lower BMI ranges. As expected, the following statements received less approval than some of the statements above:

GI surgery should be considered for the treatment of type 2 diabetes in patients who are appropriate surgical candidates with BMI < 35 who are inadequately controlled by lifestyle and medical therapy. [Was put up for vote]

GI surgery may be appropriate for the treatment of type 2 diabetes in patients who are appropriate surgical candidates with BMI < 35 who are inadequately controlled by lifestyle and medical therapy [Was put up for vote]

At this point the discussion was intentionally titrated out of bounds:

GI surgery could be considered for the treatment of type 2 diabetes in patients who are appropriate surgical candidates with BMI < 30 who are inadequately controlled by lifestyle and medical therapy. [Put up for vote; received low approval rating].

For which the research consolation proved unanimous.

In patients with a BMI < 30, determining the appropriate use of GI surgery for the treatment of type 2 diabetes is an important research priority. [Put up for vote, received unanimous approval]

After a few steps which looped back to a previous statement, the following was voted on:

GI surgery may be appropriate for the treatment of type 2 diabetes in patients who are appropriate surgical candidates with BMI of 30 to 35 who are inadequately controlled by lifestyle and medical therapy. [Put up for vote, received 82% approval]

and similar meetings, the words of my statistics professor stood out: one should write up the results (in one's head) before even beginning the experiment.

So, by the end of day two, it was pretty clear that the group as a whole would be ready to make some revised clinical recommendations on day three. Aside from this, however, it was clear that weight loss surgery research needed, at a fundamental level, to start from scratch. After seeing data presented on the topic for years and years, it was surprising to feel the situation, from the perspective of academic rigor, as one where researchers were more or less just starting out with a blank slate.

Voting Day

Voting addressed clinical guidelines first, followed by research guidelines. Voting took place using remote controlled devices, with the summary results of each vote displayed on the projector moments later. Information about the particulars of the process, including the evolution of the language used, are described elsewhere in this section.

At one point, the discussion turned to the phrasing of the 1991 NIH statement. It was noted that the meeting was completely independent from the 1991 statement and not under any obligation to conform to or update that statement. One bariatric surgeon indicated that even though the 1991 statement endorsed the use bariatric surgery in patients with a BMI between 35 and 40 who had co-morbidities, he had never done so. This provided some perspective. Here, 16 years after it was sanctioned, at least some surgeons practice more conservatively than what the NIH allowed many years ago. Carefully worded statements at one point received very low approval when the BM dipped below 30, but regained majority support when rephrased within the 30-35 range. Once the group had breathed a collective sigh of relief regarding what it recommended clinically, discussion turned to consideration of research guidelines and expectations. On the surface, this is fairly innocuous. Whether one agreed with specific treatment guidelines, very few would disagree with studying it. The importance, however, stems from the desire to get the buy-in of organizations with very high scientific standards. If the statement explicitly includes requirements that future progress be based on good science, it provides an aura of conservative security, reserve and caution. While this was well and good in concept, putting it down in writing was awkward. Here's the gist of what the panel wanted to say:

"We think future decisions should be informed by good science on the topic."—and—"We think that good science means XYZ (ex: controlled randomized studies)."

Anyone NOT endorsing the first statement sounds foolish, however the first statement depends upon the second. The second statement, for its part, reads precariously like a group of 50 making a statement on behalf of either all diabetes research or, more worrisome still, all scientists in general.

The awkwardness gave way to something worse in that those voting against a statement are not asked why. If, for instance, someone wanted studies to be both "controlled" and "randomized," but a statement included only one of the options, a no vote on that statement, it could seem that they were voting against the statement as not good at all, versus not good enough. It was proposed that the way out of this was *not* to vote against the statement, but, rather, to simply abstain from voting either way. That offered some solace, particularly since the group that would be interpreting the meaning of any such abstinence would be the same people offering it as an option.

The reality is that everyone wants evidence, and the more and the higher quality, the better. Still, evidence from non-randomized, non-controlled studies is better than no evidence at all. Scientific consensus results from rational evaluation of "all" data available at the time of analysis, whether derived from weak or robust studies. To endorse that evidence "should" be of higher value does not mean that additional evidence is completely useless if it is of lower quality. One way the statement could have gone was to say, "We won't even look at any data unless it comes from controlled, randomized trials," but no one wanted that. There was some sense that members didn't want to impose any artificially high standards that

would delay useful future progress. In the end, "randomized" was dropped from the statement and the following statement received a majority "Yes" vote:

Controlled trials should be the standard of clinical research to assess the utility of GI surgery for the treatment of type 2 diabetes. [Was put up for vote]

As discussion progressed, progress was sped along in part by a collective sense of resignation that the disadvantages of the ambiguities at hand were counterbalanced by the disadvantages of issuing no statements at all. Majority votes were reached on the following:

Standardized diagnostic and evaluative criteria for type 2 diabetes should be adopted for clinical studies in this area. [Was put up for vote]

Animal models can provide useful information about the efficacy of GI metabolic surgical procedures for the treatment of type 2 diabetes. [Was put up for vote]

A fairly tedious list of statements came next. Two statements with high agreement included one endorsing the notion that studies of diabetes and surgery be registered within a central registry, and another which called for the development of particular specific standards for measuring clinical and physiologic outcomes. At that point, a fair amount of discussion went into the question of what research should aim for. Was the goal outright cure or resolution? These were voted down in favor of more moderate aims of "remission" or long-term "control" as customary in non-surgical research of diabetes.

Coming full circle, what really matters about research criteria was a point that the resolution language itself might not have directly addressed, namely, the need to focus on statistical power for the particular hypothesis being tested. To have a study that contains randomization or a double blind aspect, or a control group doesn't mean that the right things are being randomized or double blinded or controlled. A great many studies over the years were been randomized, controlled, and even longitudinal but they aren't of much help now with respect to the current issue because neither diabetes resolution in particular nor the 30-35 BMI range in particular were targeted, up front, as the particular items for which statistical power was needed. Current and imminent research addresses this.

Pax Romana

Those expecting a major fight between surgeons and non-surgeons didn't get one. Some attendees expressed very strong concerns or disagreements at times, but these were almost always about specific particular points where they wanted to call attention to various distinctions that were being overlooked by someone else making a more general statement. For example, one non-surgeon, referring to the difference in mechanism between hepatic insulin resistance and peripheral insulin resistance, stated: "Many of these surgeons ultimately just can't get it that they can't just reach into this population and treat these lower BMI people as if they were larger over 40 BMI because they're not; they have different factors going on, on an individual by individual basis."

One voting participant, when asked to comment on the composition of the panel, seemed to validate its breadth in providing this unexpected remark: "This was a great meeting, but I'm afraid I was useless … I'm in research. I don't work with this on a clinical level. I didn't know what to say to these clinical items. They're probably wondering why they invited me." Certainly, some tension between surgeons and non-surgeons was there, but really only as an undercurrent that one almost could have missed if one hadn't been looking for it. One European voting participant offered some perspective: "These Americans are different than Europeans, you know, kind of taking their fighting here. In Europe, we don't have such strong divisions like that. That's probably because we don't have as many people involved outside of academics, or at least not that I hear about as often. Surgeons and non-surgeons at research centers tend to have more awareness of each other's areas."

One thing that the panel didn't address was the core issue of whether surgery should be philosophically considered as a primary treatment versus always being a treatment of last resort. I think that where people stand on that issue ultimately boils down to which fundamental perceptual paradigm they adopt in their younger years. Those most comfortable with the first stance are the people most likely to chose surgery as a career. It's only later in life that these choices are reinforced by professional and financial status. Granted this, however, there's no way around it: surgery for diabetes shifts the balance of power, making surgeons comparatively more important in the field and non-surgeons comparatively less important. This constitutes a shift in

How Surgery Types Compared

As one would suspect, there was plenty of discussion regarding surgery types. Regarding the BPD/DS it was implicitly clear that the degree of malabsorbtive component to this procedure was significant (which is why some surgeons view it as the surgery of choice for super-obese patients). Dr. Scopinaro, in particular, stressed that BPD and DS ought not be referred to interchangeably. Aside from that, the differences between surgery types seemed to loosely reflect the degree of familiarity or experience the voting body had as a whole with the procedure. Individuals cited efficacy statistics describing high success with both the LAGB and Gastric Sleeve. However, one surgeon said he wouldn't be able to endorse any final statement that endorsed the LAGB, a procedure he chose not to offer his patients.

Of the surgery types, LAGB is distinct in that no intestine is bypassed or otherwise altered. For this reason, it is assumed that any mechanisms for diabetes resolution involving intestinal hormone function are not likely to be relevant in the same way. This matters because even though clinical data suggests diabetes resolution with LAGB in some ways on par with that of other procedures, various official indication protocols emphasize an understanding of mechanism.

First, the fundamental nature of diabetes resolution was addressed. Is there something that surgery does that you can't get without surgery of some type? (Note, these questions were actually addressed first, before the primary sequence leading up to the concluding resolutions).

Gastrointestinal bypass procedures (RYGB, BPD, DJB, etc) can improve diabetes by mechanisms beyond changes in food intake and body weight. [Was put up for vote].

Next, the following question was asked to assess the degree of agreement that there was a physiological basis by which different surgery types had different effects. If there are different mechanisms of diabetes resolution, then it makes sense to study different surgery types individually.

Anatomic modification of various regions of the GI tract likely contribute to the amelioration of type 2 diabetes trough distinct physiological mechanisms. [Was put up for vote].

With that ground covered, adjustable gastric banding was considered in the following ways:

Adjustable gastric banding improves glucose homeostasis primarily through decreased caloric intake and weight loss. [Was put up for vote].

LAGB appears to be a promising approach for the treatment of type 2 diabetes, in patients with severe obesity, inadequately controlled by lifestyle and medical therapy. [Was put up for vote].

LAGB appears to be a promising approach for the treatment of type 2 diabetes, in patients with obesity, inadequately controlled by lifestyle and medical therapy. [Was put up for vote].

power that surgeons, as a group, are bound to favor and non-surgeons, as a group, are bound reject—all else equal. What may begin as a status issue is reinforced by very real economic factors—financial factors in which professional organizations take a keen interest. While it was impossible to ignore these financial and political motives at the professional level, it was also clear, speaking with panelists one-on-one, that these people were expressing their views firmly with the best interests of patient care at heart.

One big topic of speculation was why, after years of remaining nearly silent on the topic, the American Diabetes Association endorsed this conference now, and at the last minute at that. One line of thought is that it was just a natural progression. Dr. Rubino, the program co-director, had been working to organize this conference for about two years and had been working with Dr. Poires—a surgeon active with diabetes research—and others. Whatever the reasons in particular, there is no ignoring the coming epidemiological tidal wave. As one panelist stated: "It's either treat diabetes now, or treat super-obesity later. At some point, they're going to have to budge… In a few years there will be so many people in need of bariatric surgery, there won't be any surgeons left to do anything else."

The real question, according to inbound ASBS president Kelvin Higa, concerns the NIH. Obesity and diabetes receive such a tiny fraction of federal health research funding compared to diseases , such as AIDS, with more vocal advocates. One may wonder what the approximately 17 million diabetic individuals in the United States think about that. Theirs is a disease that tends to get worse over time, often manifesting in late middle age. Depending on where you draw the line, there are perhaps a good 12-13 million diabetics firmly within the age range where voter turnout is reliably high. This should be a powerful political bloc and, along with economic realities, raises the question of how relevant academic consensus will ultimately become. To the degree that diabetic individuals embrace surgical treatment and are able to expose their primary care providers to the treatment modality, practice patterns may evolve with or without the full and active endorsement of the clinical academic elite.

Pyrrhic Victories

There's been an interesting BMI dance going on over the years, with groups of researchers missing one another in the night, so to speak. First, the bariatric surgery community has relished clinical studies that showed how being overweight was associated with adverse health and economic consequences. The stronger that association, the stronger the case for bariatric surgery. Indeed, huge piles of data came forth over the course of many years which definitively linked being overweight with these adverse consequences, but the victory was pyrrhic. Even to this day the vast bulk of the data is all but useless to bariatric surgery because almost none of it has taken BMI 35+ levels specifically into consideration. The very high BMI category was never targeted by these studies, which typically included "30 and over" as one of two or three ranges. This is tragic, because the adverse consequences of obesity are so markedly severe the very high BMI ranges. The whole obesity research process of the past two decades failed to target the one BMI category (35+) where it could arguably have done the most good from a practice and policy perspective.

This was followed by yet another pyrrhic victory, but this time from another direction. Bariatric surgery studies focusing predominantly on patients with a BMI of 40+ have made it conclusively clear that gastrointestinal surgery improves or resolves diabetes. That evidence has made health plan refusal to cover surgery nothing less than blatantly economic in motive. However, as addressed earlier, hardly any of these studies specifically targeted patients with BMIs of 30-35, controlled by

surgery type, with sufficient statistical strength. So, if gastrointestinal surgery has the greatest potential to do the greatest good for the greatest number of (diabetic) people who could benefit, the vast majority of these people are firmly outside the BMI regions best researched.

This is an ironic twist of sorts. While so much research data has been published by non-surgeons over the years showing the adverse effects of obesity, very few of these studies ever bothered to single out the extent of the adverse effects at the 40+ BMI range—even though, in aggregate, they collectively contained a large number of such individuals, stranded, so to speak, within many statistically effete tail-ends. Now, as the surgery loops back into a traditionally clinical arena, the block is that surgery literature did not (for various and often understandable reasons) do much to address the end of the spectrum below BMI 35. It seems, then, that science has failed both the patients with very high BMIs those with typical lower-BMI diabetes, the very patients who continue to stand the most to benefit from science. It would seem that science could best contribute to patient wellbeing by getting more of the high BMI into obesity research while taking the high BMI out of diabetes surgery research.

This "packaging" of data sets (what's in the spotlight versus what's in the periphery data bins) is analogous to packaging on a more political front. Consider the two statements:

Statement #1: Surgery is appropriate for people who have a 35-40 BMI and who just also happen to have diabetes as well.

Statement #2: Surgery is appropriate for people who have diabetes and who also just happen to have a 35-40 BMI as well.

In a very real sense, this attentive slight of hand is what the debate is really about. When panelists pointed out that the discussion had "finally caught up to" the 1991 statement they were correct, but they were also incorrect. Just at the point that thousands of surgeons have made the somewhat awkward journey toward becoming proud "bariatric" surgeons, these surgeons might soon be able to do the greatest good by staunchly de-emphasizing the term "bariatric" as much as possible. When debate turned to what to call the surgery in question (i.e.,"GI metabolic surgery" vs. "GI surgery"), no one wanted to refer to the surgery as "bariatric surgery"; that would, in essence, defeat the primary conceptual agenda.

I'm taking bets on when the term "diabetic surgeon" will first appear in local print ads. Surgeons were at first very reluctant, but they too are now completely imbued with both the rhetoric and practice of comprehensive multidisciplinary follow-up care. How interesting to think that these same surgeons (and their teams), in simply following their habits, might now wind up becoming the primary advocates of such comprehensive care for lower-BMI diabetic patients where food addiction might never have been so much of problem. One almost wonders how many bariatric surgeons will wind up going back to the traditional focus on immediate anatomy alteration, rather than long-term behavior and success. In summary, the DSS conference brought issues to light that force one to put things into perspective not only at the clinical and research level, but within the realm of semantics and treatment philosophy as well. ■

Who Was Voting?—DSS Voting Panelists

Of 49 voting members below, 17 were surgeons (35%) and 25 were from the United States (51%)

	Individual	Location	Surgeon	USA
	Program Directors			
1	Francesco Rubino, MD	Catholic University of Rome, Italy	X	
2	Phillip R. Schauer	Cleveland Clinic, Cleveland OH	X	X
3	Lee M, Kaplan	Harvard Medical School		X
4	David Cummings	University of Washington, Seattle, WA		X
	Clinical and Research Guidelines Development			
5	Aureo De Paula	Hospital De Especialidades, Goiania, Brazil		
6	David Kelley	University of Pittsburg, USA		X
7	Samuel Klein	Washington University, USA		X
8	Carel LeRoux	Imperial College, London, England		
9	Geltrude Mingrone	Catholic University of Rome, Italy		
10	Walter Pories	East Carolina University, USA	X	X
11	Richard Denis Laval	University, Canada		
12	Stephan Sauerland	University of Cologne, Germany	X	
13	Nicola Scopinaro	University of Genoa, Italy	X	
14	Harvey Sugerman	Editor-in-Chief, SOARD, USA	X	X
	Voting Panel Members			
15	Garth Ballantyne	Hackensack University, USA		X
16	Steve Bloom	Imperial College of London, England		
17	Camillo Boza	Catholic University of Santiago, Chile		
18	Henry Buchwald	University of Minnesota, USA	X	
19	Ricardo Cohen	Hospital Sao Camilo, Sao Paulo, Brazil	X	
20	David D'Alessio	University of Cincinnati, USA		X
21	John Dixon	Monash University, Melbourne, Australia		
22	Franco Favretti	Ospedale Maggiore, Vicenza, Italy	X	
23	Ele Ferranini	University of Pisa, Italy & President EASD		
24	Gema Frühbeck	University of Navarra, Spain		
25	David Flum	University of Washington, USA	X	X
26	Michel Gagner	Cornell Universiy, New York, USA	X	X
27	Giovanni Ghirlanda	Catholic University, Rome, Italy		
28	Alison Goldfine	Harvard Medical School, Boston, USA		X
29	Peter Havel	University of California, Davis, USA		X
30	Bill Herman	University of Michigan, USA		X
31	Kelvin Higa	University of California San Francisco, USA	X	X
32	Jacques Himpens	Saint Pierre University, Bruxelles, Belgium	X	
33	Jens Holst	University of Copenhagen, Denmark		
34	Van Hubbard	National Instututes of Health (NIH) USA		X
35	Judith Korner	Columbia University, New York, USA		X
36	Antonio Lacy	University of Barcelona, Spain	X	
37	Michael Meguid	SUNY Upstate Medical University, USA		X
38	Jerry Palmer	University of Washington, USA		X
39	Michel Pinget	University of Strasbourg, France		
40	Antonio Pontiroli	University of Milan, Italy		
41	Eric Ravussin	Pennington Biom. Res. Center, USA		X
42	Itamar Raz	Hadassah University Hospital, Israel		
43	William Richards	Vanderbilt University, USA	X	X
44	Donna Ryan	Pennington Biom. Res Center, USA		X
45	Randy Seeley	University of Cincinnati, USA		X
46	April Strader	University of Southern Illinois, USA		X
47	Richard Stubbs	Wakefield Gastroenterology Centre, NZ	X	
48	Tessa Van der Merwe	Univ. of Pretoria, South Africa		
49	Bruce Wolfe	Oregon Health and Science University, USA	X	X
		TOTAL	**17**	**25**