Bariatric Surgery, Exercise, and Inpatient Glycemia Treatment

The American Diabetes Association's 57th Annual Advanced Postgraduate Course

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Bariatric surgery in diabetes

Lee Kaplan (Boston, MA) discussed new information based on studies of bariatric surgery in diabetes. Surgery is performed in 0.25% of Americans with obesity, so it is unlikely that it in itself can address the U.S. diabetes or obesity issues, but lessons from its use may shed light on the approach to obesity and diabetes for the overall population. The biology of obesity suggests that it is caused by inactivity and overnutriton and likely stress as well. There is a huge burden of obesity-associated illness, including malignancy, and obesity has a devastating effect on quality of life and also on what is termed societal "efficacy" and socioeconomic status. The physiology of obesity involves central regulation of food intake, nutrient handling, and energy expenditure, with adipose tissue energy stores regulating levels of signals such as leptin, and information from liver, muscle, and bone on metabolic needs coupled with information from the gastrointestinal tract and sensory organs regarding the quantity and quality of nutrient intake. A unifying theme is the body's defense of fat (rather than of total body weight).

Surgery includes the Roux-en-Y combination gastric restriction and bypass (RYGB) of distal stomach, duodenum, and proximal jejunum, which is the most effective, and may be the most appropriate, for diabetes treatment. Adjustable gastric banding is a gastric restriction procedure, while vertical sleeve gastrectomy removes the greater curvature of the stomach, acting in a fashion very different from gastric banding, causing more rapid gastric emptying. In the Swedish Obesity Study, lifestyle was compared with bariatric procedures. Gastric banding led to ~20% weight loss initially, which decreased to 14% after a decade. RYGB led to 38% weight loss initially, decreasing to 28% at 10 years. Lifestyle modification led to an initial weight loss of 7%, dropping to 2% at 10 years. Gastric bypass improved all and cured 18% of diabetes (1). In a retrospective cohort study of 9,949 patients who had undergone gastric bypass surgery and 9,628 severely obese individuals who applied for driver's licenses in Utah, a 7.1-year follow-up of 7,925 age-, sex-, and BMI-matched pairs showed mortality reduction of 40%, with 56% less coronary disease–related mortality (2). There are, of course, adverse outcomes, and neither study was a randomized controlled trial. Currently accepted indications for surgery in individuals for whom other approaches to weight loss have failed are *1*) BMI >40 kg/m^2 or 2) BMI >35 kg/m^2 with major medical complications of obesity. A total of 250,000 such operations are performed annually in the U.S.—far fewer than the 10 million people who fill these criteria. Contraindications include severe cirrhosis, unstable coronary disease, psychiatric illness, noncompliance, and substance abuse.

It is not clear, Kaplan pointed out, why gastric bypass is so effective. It appears to alter both endocrine and neuronal gastrointestinal signals to the brain, pancreas, and liver rather than just exerting a mechanical effect in decreasing food intake. Dramatic effects on hunger and satiety are seen, but few patients become underweight and then usually only in association with major surgical complications. Because the improvement in metabolism often reestablishes ovulation, it is noteworthy that there is weight gain in women who have had the procedures and then become pregnant. When the procedures are carried out in thin people or in animals, weight loss does not occur. Changes are variously reported in endocrine markers such as ghrelin, peptide YY, glucagon-like peptide-1, and glucose-dependent insulinotropic polypeptide, and bariatric surgery causes increased energy expenditure. It may, then, increase the effectiveness of gastrointestinal signals and, hence, physiologically create an overfed state that leads to weight loss to attain a new set point. In contrast to the improvements seen after surgery, with diet, appetite increases, energy expenditure decreases, and stress responses increase. RYGB reduces food intake and changes food preference, central dopamine signaling, energy expenditure, insulin sensitivity, pancreatic β-cell biology, lipid metabolism, and gastrointestinal mucosal remodeling. Its effects on diabetes are profound, with the condition resolving in 45% of patients after gastric banding, 85% after sleeve gastrectomy or gastric bypass, and 98% after the more radical bilio-pancreatic diversion, correlating with weight loss after gastric band procedures but exceeding the degree of weight loss with the latter three approaches, perhaps because of changes in gastrointestinal hormone signaling independent of weight loss.

In an animal model, RYGB induces weight loss from reduction in fat mass and fasting glucose improves, as does glucose tolerance. In a relatively lean animal model of insulin resistance and diabetes, comparing diet-induced and RYGB weight loss, both reduce development of fasting hyperglycemia, but patients un-

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dergoing surgery have less glucose intolerance, with an increase in islet cell mass and improvement in histology and insulin content.

RYGB involves gastric restriction, altered gastric function, and exclusion from the digestive pathway of the distal stomach, duodenum, and proximal jejunum. With use of a plastic sleeve to exclude the mucosa of the duodenum and jejunum, weight, fasting glucose, and insulin levels decrease while insulin sensitivity increases, mimicking many aspects of RYGB; such an approach is now being explored with an endoluminal duodenal barrier as a bariatric therapy. Gastric surgery alone changes weight and food intake but has little effect on energy expenditure and glucose metabolism, while duodenal barrier and ileal interposition procedures have less effect on weight and food intake and more effect on energy expenditure and glucose metabolism, with RYGB affecting all these parameters. Reasoning that "efficacy has to be matched against risk and cost," Kaplan suggested that the procedures have benefits outweighing risk, although he does not recommend gastric banding because 20% of patients undergoing this procedure subsequently require RYBG, which then has markedly increased risk. It may be possible, he suggested, to devise approaches with multiple pharmaceutical, nutritional, and "nutriceutical" agents, perhaps also using endoscopically placed devices to mimic the effects of surgery.

Exercise for diabetes

Judith Regensteiner (Aurora, CO) discussed prescription of exercise for diabetes, noting decreased ability to exercise among diabetic individuals even early in the disease, perhaps related to underlying cardiac abnormality, leading to a vicious cycle of physical inactivity perpetuating insulin resistance. The Diabetes Prevention Program and Finnish Diabetes Prevention Study participants who did not lose weight but were physically active were protected to some extent from developing diabetes. Discomfort during exercise, Regensteiner noted, is more often perceived by diabetic than by weight-matched nondiabetic individuals, without clear explanation, but posing a barrier to exercise for diabetic patients. Diabetes is associated with reduction in maximal oxygen uptake, a clinically relevant cardiovascular fitness marker. Diabetic women show reduced exercise tolerance, but this may be particularly improved in these patients as opposed to in those without diabetes, as demonstrated in a trial of exercise training (3). Diabetic women in a supervised aerobic and resistance training intervention 3 days per week for a period of 10 weeks had improved oxygen consumption and large artery compliance in another study (4). In a comparison of diabetic women with healthy control women, the major difference was in increased pulmonary capillary wedge pressure during exercise, suggesting diastolic dysfunction/heart stiffness. Nuclear stress testing showed decreased total myocardial perfusion, correlating negatively with pulmonary capillary wedge pressure, an apparent cardiac abnormality seen early in diabetes (5). Echocardiographic studies of type 2 diabetic and obese adolescents have shown a correlation between decreased insulin sensitivity and reduction in oxygen utilization, and Regensteiner speculated that insulin resistance might be causally related to the cardiac abnormalities (6).

Physical activity has been shown to improve cardiovascular risk and reduce mortality in diabetic patients in cross-sectional studies (7). In the National Health Interview Survey, an 8-year follow-up of 2,896 adults with diabetes showed that those who reported walking 3–4 h weekly, or those who reported sufficiently strenuous walking to increase their heart and breathing rates, had ~50% lower mortality, regardless of sex, age, race, BMI, diabetes duration, comorbid conditions, and physical limitations (8). A meta-analysis of 14 controlled trials of exercise in diabetic individuals showed an A1C reduction from 8.3 to 7.7% but no significant weight loss, further suggesting potential benefit (9).

Why, Regensteiner asked, does exercise help? Exercise improves endothelial function (10), and acute episodes of exercise may increase tissue blood flow, with the resulting shear stress stimulating nitric oxide synthesis. Exercise may reduce inflammation and appears to decrease abdominal visceral fat (11), with the consequent improvement in body composition perhaps being more important than weight loss per se in improving insulin sensitivity. "Exercise," she concluded, "is medicine—it's free medicine!" Rather than recommending vigorous exercise, as previously suggested, the current physical activity guidelines suggest at least 30 min of moderate-intensity physical activity at least 5 days weekly, and in addition to that adults should perform muscle-strengthening exercises (12). Aerobic exercise should be performed five times weekly at 55–85% of the maximal heart rate, calculated as 220 − age, and resistance exercise twice weekly, with 12–15 repetitions at an intensity of one-third to one-half of the one-repetition maximal, performing 8–10 different exercises. For children, twice as much activity is recommended, as well <1 h daily of television plus computer time. Walking is particularly recommended. The average in the U.S., in a study of 111 individuals wearing pedometers, was 4,000–5,000 steps daily, with a reasonable goal of 10,000 steps daily (13). The use of a pedometer may be helpful in giving patients a sense of accountability, although it is then important that the health care professional review the exercise log. She suggested that appropriate footwear, attention to blood pressure control, appropriate advice for prevention of hyper- and hypoglycemia, and avoidance of heavy straining for individuals with retinopathy are all reasonable. Regensteiner reviewed indications for cardiac stress testing, suggesting that this be done with typical or atypical cardiac symptoms, resting electrocardiogram abnormality, and peripheral or carotid arterial disease and in individuals with a sedentary lifestyle who plan to begin vigorous exercise. She pointed out that exercise tests are often abnormal with diabetic cardiomyopathy, cardiovascular autonomic neuropathy, and renal insufficiency, with such individuals requiring echocardiographic or nuclear stress testing.

Glycemic control in hospital

Mary Korytkowski (Pittsburgh, PA) discussed glycemia control in hospitalized patients, addressing the glycemic targets and appropriate approaches. "The study that really reawakened the medical community" by Van Den Berghe in 2001 laid to rest the notion that the most important aspect of diabetes treatment was simply the avoidance of hypoglycemia, showing that intensive glycemic management reduced requirement for ventilatory support, transfusion, dialysis, and sepsis treatment and, most impressively, reduced intensive care unit mortality (14). Glucose levels in the intensively treated group were maintained between 80 and 110 mg/dl, whereas the control group levels were ~200 mg/dl, leading many to express concern about risk of hypoglycemia. Reanalysis of the study, however, did suggest particular benefit in the group

with optimal control (15). Similar studies from this group have shown a beneficial effect of intensive treatment in infants and children, with reduction both in infections and in mortality. In this study, however, hypoglycemia occured in 4.9% of intensively treated patients, but in 0.9% of control subjects, showing the need for careful monitoring (16). Subsequent studies have not clearly shown benefit, with evidence of adverse effect, but interpretation of the studies is complicated by six- to eightfold higher rates of hypoglycemia and by lesser difference in glycemia between the intervention and control groups (17–19). In the large, international, randomized trial Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR) comparing mean glucose levels of 118 vs. 145 mg/dl during the typical 4–5 day period of insulin infusion, hypoglycemia, defined by glucose <40 mg/dl, occurred in 6.5 vs. 0.5% of patients, respectively, and 90-day mortality was 14% greater with intensive glycemic treatment at 27.5 vs. 24.9%, leading to the conclusion, "the guidelines needed to change" (20). Korytkowski noted the far later occurrence of mortality than of hypoglycemia, leading to the "open question": what was the mediator of the adverse outcome? A meta-analysis that included NICE-SUGAR showed no significant benefit of intensive insulin treatment (21). Korytkowski asked the audience, however, to "remember that conventional therapy was not really poor control" but, rather, a mean level of 140–150 mg/dl. Explanations abound, including variability in insulin-management protocols, the difference between multicenter and individual center studies, arterial versus venous versus capillary glucose monitoring, laboratory testing versus point-of-care glucose meters, and variability in the duration of hyperglycemia prior to randomization. The original Leuven study comprised a postoperative group, so the onset of hyperglycemia could be completely eliminated. Sepsis was prevented in the Leuven study, while patients already having severe sepsis, Korytkowski said, "may in fact be too ill for intensive insulin therapy." A study of 12 healthy males injected with lipopolysaccharide to produce endotoxemia showed an increase in insulin sensitivity at the liver and periphery (22); individuals with sepsis would require particular caution in insulin administration. Point-of-care glucose meters have shown variability of up to 32% from laboratory glucose measures, which would of course be a major issue in titrating intravenous insulin for intensive glycemic control. Whole blood, polycythemia, oxygen, and acetaminophen decrease glucose readings with various methodologies, whereas anemia and other factors may increase glucose readings.

There is no doubt that hypoglycemia increases levels of cortisol and epinephrine, and also of cytokines such as interleukin-1β, interleukin-8, and tumor necrosis factor-α (23), and so "could undo the benefits." Hypoglycemia is associated with increased hospital length of stay (24). Is there, then, any reason to pursue glycemic control in critically ill patients? Comparing poor with excellent glycemic control, there is a marked increase in post-sternotomy wound infection (25) and in total infection rates (26) and a progressive increase in mortality (27). It may be that an appropriate glycemic target is that of the conventional treatment group in NICE-SUGAR: insulin was started for glucose >180 mg/dl, and a mean glucose level of 144 mg/dl was achieved. Intravenous insulin, Korytkowski stated, should start at 140–180 mg/dl, using a proven safety/efficacy protocol with acceptable ease of use and incidence of hypoglycemia.

What of patients outside critical care units? Hyperglycemia is associated with increase in mortality, and this is particularly so for those with new-onset hyperglycemia rather than for patients with established diabetes (28). During exacerbation of chronic obstructive lung disease, a stepwise increase in adverse outcome has been seen at glucose levels of <108, 108–124, 125–160, and >160 mg/dl (29). We need, then, to "identify reasonable, achievable, and safe glucose targets." A reasonable recommendation is that of the American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control, aiming for levels of 140–180 mg/dl in general and 110–140 mg/dl in cardiothoracic intensive care unit patients, with 100–140 mg/dl premeal and other levels <180 mg/dl. Hospital hyperglycemia is currently being defined as any glucose >140, with stress hyperglycemia refering to elevated glucose in patients without prior history of diabetes, for which one may use A1C <6.5% in screening (with appropriate cautions as to factors affecting A1C). Hypoglycemia is defined as <70 mg/dl and severe hypoglycemia <40 mg/dl. "How," Korytkowski asked, "do we get there safely?" In non–critically ill patients, insulin is preferred as scheduled basal-bolus therapy with correctional components rather than treatment with sliding-scale insulin. Insulin is preferred because sulfonylureas cause hypoglycemia, particularly with variable meals, metformin is often contraindicated, thiazolidinediones cause edema and heart failure and require weeks to months for onset of glycemic action, α-glucosidase inhibitors are relatively weak, and pramlintide and glucagon-like peptide-1 agonists can cause nausea and exert greater postprandial effect. An approach is to institute treatment with a total daily dose of 0.2–0.4 units/kg body wt, with 50–60% as basal insulin, using correction insulin for glucose levels above goal and adjusting according to results of bedside glucose monitoring. Such regimens lead to better mean glycemia without increase in hypoglycemia compared with sliding scale–only treatment approaches (30), and the use of insulin analogs leads to less hypoglycemia than do human and NPH insulin (31).

Enteral or parenteral nutrition and glucocorticoid therapy are predictors of risk of hyperglycemia with and without known diabetes, so one should monitor glucose in these patients and administer insulin accordingly, recognizing the need to adjust insulin proactively as nutrition treatment or glucocortocoid doses are modified both in the hospital and when a patient on such treatment is discharged. Korytkowski reviewed her study of patients starting enteral nutrition, which shows a reduction in hypoglycemia with insulin glargine given prospectively rather than a human or NPH insulin regimen (32). She suggested that for the special case of patients receiving insulin pump treatment, it is reasonable that patients continue such treatment "provided they have the mental and physical capacity to do so" but with available hospital personnel with expertise in the use of pumps and with a formal inpatient insulin pump protocol to reduce confusion and treatment variability (33).

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