

rHuPH20, increases the absorption and dispersion of injected drugs. The Phase 3 Linjeta trial [NCT01067118] failed to meet criteria for noninferiority versus a comparator, and optimal temperature, timing, duration of the warming period, and the effect on infusion set age have yet to be determined for the warming device used in the study.

Each of the new approaches has shown positive results, based on pharmacokinetic and pharmacodynamic studies. However, each has its own issues regarding safety and practicality, and none has been shown to have enhanced clinical efficacy for open-loop therapy. Nevertheless, the future potential of several of these approaches in providing insulin absorption and action profiles that more closely simulate that of the normal β -cell is quite promising and complement research that is directed at the development of closed-loop insulin delivery systems.

The LOOK Ahead Trial: Four-Year Outcomes of an Intensive Lifestyle Intervention in Type 2 Diabetes

Written by Lori Alexander

The primary objective of The Action for Health in Diabetes (Look AHEAD) Trial is to examine the long-term effects of an intensive lifestyle intervention (ILI) that is designed to achieve and maintain weight loss by decreasing caloric intake and increasing physical activity in overweight or obese volunteers with type 2 diabetes. Participants in this program will be compared with controls who are involved in diabetes support and education (DSE, usual care).

A multicenter, randomized, controlled trial on the long-term (13.5 years) effects of ILI on cardiovascular morbidity and mortality (ie, the incidence of cardiovascular disease [CVD], death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization) in this population. The study includes 5145 participants and is planned through June 30, 2015.

Xavier Pi-Sunyer, MD, St. Luke's Roosevelt Hospital Columbia University, New York, New York, USA, described the study design in detail, as well as key results over 4 years [Look AHEAD Research Group et al. *Diabetes Care* 2007; Look AHEAD Research Group et al. *Arch Intern Med* 2010].

Averaged across 48 months, ILI participants had a greater percentage of weight loss than DSE participants (-6.15% vs -0.88%; $p < 0.001$) and greater improvements in treadmill fitness (12.74% vs 1.96%; $p < 0.001$), HbA1C level (-0.36% vs -0.09%; $p < 0.01$), systolic (-5.33 vs -2.97 mm Hg; $p < 0.001$) and diastolic (-2.92 vs -2.48 mm Hg; $p = 0.1$) blood pressure, and levels of high-density lipoprotein cholesterol (3.67 vs

1.97 mg/dL; $p < 0.001$) and triglycerides (-25.56 vs -19.75 mg/dL; $p < 0.001$) [Look AHEAD Research Group et al. *Arch Intern Med* 2010].

Reductions in low-density lipoprotein cholesterol were greater in DSE than ILI participants (-12.84 vs -11.27 mg/dL; $p = 0.009$), due to greater use of lipid-lowering medications in the DSE group. At 4 years, ILI participants maintained greater improvements than DSE participants in weight, fitness, HbA1C levels, systolic blood pressure, and high-density lipoprotein cholesterol levels [Look AHEAD Research Group et al. *Arch Intern Med* 2010].

Pediatric Weight Loss Surgery: Is It Time?

Written by Rita Buckley

Over the past 20 years, the rate of obesity or overweightness (>95th percentile for age and gender) has doubled among children and tripled among adolescents, affecting more than 5 million of them in the United States alone [O'Brien PE et al. *JAMA* 2010]. This increase has been accompanied by a dramatic rise in obesity-related health complications, including illnesses that threaten life expectancy in the absence of significant weight loss [Sarwer DB, Dilks RJ. *J Youth Adolescence* 2011]. To date, there are no medical therapies that provide significant and durable weight loss [Barnett SJ. *Curr Opin Pediatr* 2011].

Paul O'Brien, MD, Monash University, Melbourne, Australia, discussed weight loss surgery in the pediatric population. The central question that he addressed was: "Is it time?" His answer was a definitive yes. In fact, he believes it is overdue.

Prof. O'Brien discussed the variety of procedures that are available—including the laparoscopic adjustable gastric band, sleeve gastrectomy, Roux-en-Y gastric bypass (RYGB), and biliopancreatic diversion with duodenal switch. Based on invasiveness, risk, complexity, and problems, he rated them on a scale of 1 to 10, with gastric banding a 5.0 (Table 1; Figure 1).

According to Prof. O'Brien, the gastric band increases satiety and is a safe, effective, gentle, and cost-effective option that improves quality of life. In a recent study that compared the gastric band with an optimal lifestyle intervention, he and his colleagues found that 84% of obese adolescents in the surgery group and 12% in the lifestyle group lost >50% of excess weight, corrected for age. At entry, 36% of participants in the surgery group and 40% in the lifestyle group had metabolic syndrome. At 24

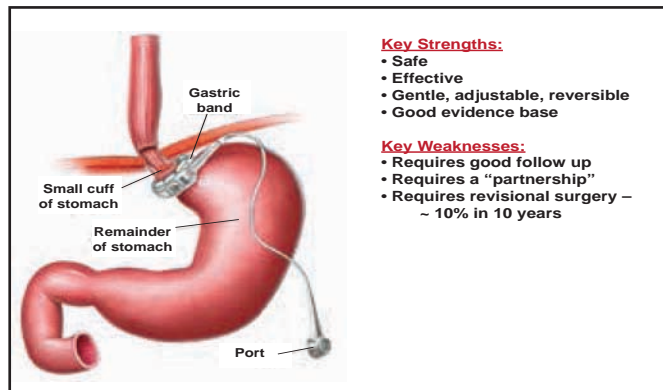
months, none of the adolescents who underwent surgery had it ($p=0.008$) compared with 22% in the lifestyle group ($p=0.13$) [O'Brien et al. *JAMA* 2010].

Table 1. Hierarchy of Weight Loss Techniques.

Therapy	Rating
Lifestyle - Eat less and do more	1.0
Drugs, Very low calorie diets	2.0
Endoscopic - intragastric balloon et al	4.0
Gastric banding	5.0
Sleeve gastrectomy	7.0
Laparoscopic RYGB	7.5
Open RYGB	8.5
Open biliopancreatic diversion (BPD)	9.0
Laparoscopic BPD	10.0

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Figure 1. Laparoscopic Adjustable Gastric Band.



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In adolescents, established type 2 diabetes is a strong indication for weight loss surgery [Xanthakos SA, Inge TH. *J Pediatr* 2007; Pratt JSA et al. *Obesity* 2009]. Observational studies suggest that surgically induced weight loss may be an effective treatment for the disease.

An unblinded, randomized, controlled trial in adults [Dixon JB et al. *JAMA* 2008] found that 73% of patients in the surgical group achieved remission of type 2 diabetes versus 13% in the conventional therapy group. Meta-analyses by Buchwald et al. [*Am J Med* 2009] and Maggard et al. [*Ann Surg* 2005] found similar outcomes. In adolescents, O'Brien et al. [*JAMA* 2010] found that homeostasis model assessment-insulin resistance in the surgical group fell significantly from 2.94 to 0.95 after gastric banding versus 3.17 to 1.8 in the nonsurgical group.

Prof. O'Brien cited Centers of Research Excellence (CORE) criteria for pediatric weight loss surgery. They include age >14 years; body mass index >35 kg/m² (almost always above the 99th percentile); at or near full skeletal and

developmental maturity; failure in conventional programs; and an ability to understand the process and partner with the treatment team.

He noted the need to follow the CORE indications, put together a knowledgeable and caring treatment team, make sure the kids know the rules, and collect data to measure the outcomes and learn.

Immunomodulatory Therapy Trials in Type 1 Diabetes

Written by Lori Alexander

As type 1 diabetes continues to be a worldwide epidemic, researchers persist in exploring new ways to prevent the disease from developing or to delay its development, especially in young children. Several studies have evaluated the safety and efficacy of immunomodulatory therapies, both as prevention strategies and as interventions for new-onset disease.

No studies to date have demonstrated effectiveness in preventing diabetes. In the Diabetes Prevention Trial-Type 1 (DPT-1), oral insulin did not prevent or delay diabetes in subjects who were at increased risk for the disease. However, when subsets of subjects with high insulin autoantibody (IAA) levels were analyzed, there was a 4.5- to 5-year delay (IAA levels ≥ 80 nU/mL) and a 10-year delay (IAA levels ≥ 300 nU/mL) [Skyler JS et al. *Diabetes Care* 2005]. This finding suggests a clinically meaningful benefit for a specific subpopulation, said Desmond Schatz, MD, Diabetes Center, University of Florida Health Science Center, Gainesville, Florida, USA.

In intervention studies, treatment with anti-CD3 (rituximab) led to significantly higher C-peptide levels (measured as the area under the curve) compared with controls for up to 1 year, as well as lower HbA1C levels and lower insulin dose ($p<0.001$ for all) [Pescovitz MD et al. *New Engl J Med* 2009]. Dr. Schatz said that the study indicated an immunological effect, in that the treatment completely depleted CD19 cells, with a near recovery of β -cells over the course of a year. An important finding was that the difference in outcomes between the treatment and control groups began at 3 to 6 months after the initiation of treatment. Dr. Schatz noted that anti-CD20 (teplizumab) and DiaPep277 (a synthetic heat shock protein 60 peptide) also led to significantly higher C-peptide levels, with the difference also emerging at 3 to 6 months [Herold KC et al. *New Engl J Med* 2002; Herold KC et al. *Diabetes* 2005]. These data suggest that the effectiveness of a prevention strategy could be identified early.