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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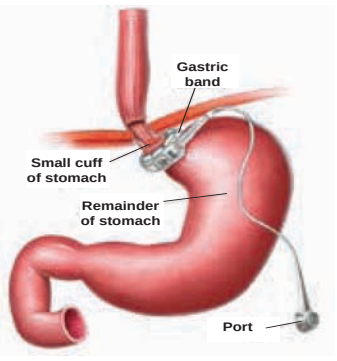
Figure 1. Laparoscopic Adjustable Gastric Band.



Key Strengths:
- Safe
- Effective
- Gentle, adjustable, reversible
- Good evidence base

Key Weaknesses:
- Requires good follow up
- Requires a "partnership"
- Requires revisional surgery – ~ 10% in 10 years

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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 unblended, 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/m^2 (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.

Dr. Schatz and his colleagues explored the use of autologous cord blood for stem cell therapy. He explained that cord blood has a high capacity for T cell regulation, has a greater regenerative capacity than bone marrow, and has been used effectively for other autoimmune diseases. In addition, cord blood may be naïve to the environmental insult that initiated the autoimmunity and, therefore, induce tolerance. The researchers' Phase 1 study enrolled 24 young children who received a transfusion when they were aged a mean of 5.25 years (range: 3.1 to 7.3 years). The treatment substantially reduced HbA1C levels and insulin requirements, which were maintained through 2 to 2.5 years of follow-up [Haller MJ et al. *Diabetes Care* 2009]. The level of regulatory T cells increased between 0 and 6 months, which suggested that the treatment favored a regulatory/protective immune response, said Dr. Schatz. He pointed out that the results should be interpreted with caution, as a limitation of the study is the use of historical controls as the comparator group.

The results of these studies are encouraging, but none of the treatments has improved insulin production, which is necessary to reverse the disease process. The one exception is a study in which nonmyeloablative stem cell transplantation increased insulin production in a study of 15 subjects (aged 14 to 31 years) with new-onset diabetes, with significant increases in C-peptide levels that were maintained at a mean of nearly 30 months of follow-up. Most subjects were insulin-independent and had good glycemic control [Voltarelli JC et al. *JAMA* 2007; Couri CE et al. *JAMA* 2009]. Despite the positive results, Dr. Schatz noted that the potential morbidity and mortality of the approach may be unacceptable.

New Biomarkers Needed for Early Diabetic Nephropathy

Written by Rita Buckley

Nephropathy is a major complication of diabetes, and its incidence has been increasing despite improvements in renal protection and glycemic control. Thus, it is crucial to identify patients who are at risk for early diabetic nephropathy and to develop preventive interventions. Since the 1980s, microalbuminuria has been an early marker of progressive kidney disease in diabetes, and although this marker is a "great example of predictive validity, [it] is no longer predictive on its own," said Bruce Perkins, MD, MPH, University Health Network, Toronto, Ontario, Canada. Instead, he said, early progressive glomerular filtration rate (GFR) loss should be the focus, and new biomarkers must be identified.

Dr. Perkins noted that several studies have indicated that microalbuminuria is a functional abnormality in diabetes and remits to normoalbuminuria over time in most patients. Although it was once thought that renal function decline was a late-occurring event that was associated with proteinuria, later studies have indicated that the initiation of renal function decline occurs soon after the onset of microalbuminuria and is not conditional on progression to proteinuria.

Early GFR loss begins at the onset of microalbuminuria in about 30% of patients with type 1 diabetes, said Dr. Perkins, and "represents a committed step—a point of no return," with the constant loss of renal function leading to advanced stages of chronic kidney disease. However, early GFR loss does not have very good agreement with the degree of microalbuminuria or its subsequent course.

In contrast, serial measurements of serum cystatin C can accurately assess GFR changes over time. Cystatin C is a nonglycosylated basic protease inhibitor that is produced by all nucleated cells, and it has estimated GFR well, even in patients with normal or elevated renal function [Cherney DZ et al. *Diabet* Med 2010]. Dr. Perkins said that taking serial measurements of cystatin C over time is one improved strategy for predicting the risk of diabetic nephropathy.

Another strategy for predicting the risk of renal disease is to find an accurate and reliable single measure, and Dr. Perkins noted that several urinary and systemic factors have been associated with subsequent early GFR loss. For example, early GFR loss has been associated with urinary excretion of some advanced glycation end products and chemokines, urinary proteomics, and tubular markers.

With regard to systemic factors, in patients with type I diabetes, high levels of soluble tumor necrosis factor receptors are strongly associated with decreased renal function, and serum uric acid concentrations at the high end of the normal range have been associated with impaired renal function in patients, with effects that are independent of those of microalbuminuria [Niewczas MA et al. *Clin J Am Soc Nephrol* 2008; Rosolowski ET et al. *Clin J Am Soc Nephrol* 2008]. Dr. Perkins said that these findings suggest that it may be possible to slow renal function loss in patients with early diabetic renal failure through the use of anti-TNF drugs and therapies that reduce serum uric acid.

Dr. Perkins emphasized the need for research to identify biomarkers for early GFR loss. Research must move beyond the reporting of associations between factors and renal failure to determine biomarker thresholds through diagnostic study methodology. Studies should also be conducted to determine the mechanisms of early GFR loss and to discover therapies that slow this loss.