- Severe retinopathy: OR=5.057 (95% CI, 1.380 to 18.537; p=0.014)
- Maculopathy: OR=4.443 (95% CI, 1.925 to 10.253; p<0.001)

The data from the two studies suggest that OSA may play an important role in the development of both diabetic neuropathy and retinopathy. Prospective studies are needed to confirm this hypothesis. In addition, research is needed to determine the impact of treating OSA on both diabetic complications.

Insulin Delivery: Special Needs of Adolescents

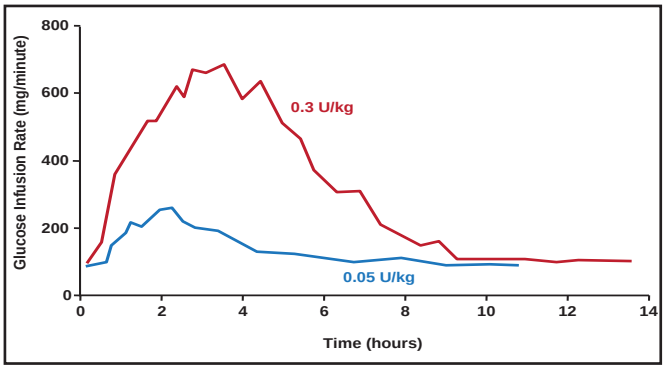
Written by Rita Buckley

In youth with type 1 diabetes (T1DM), increasing insulin resistance and decreased adherence to diabetes management tasks often occur during the adolescent years, leading to deterioration of glycemic control [Maffeis C et al. *Pediatr Diabetes* 2011]. William V. Tamborlane, MD, Yale School of Medicine, New Haven, Connecticut, USA, discussed the pharmacokinetic and pharmacodynamic properties of insulin, the need for fast-acting insulin in the pediatric T1DM population, and the latest approaches for accelerating the time-action profile of insulin.

Insulin sensitivity is reduced, even in healthy lean adolescents as they progress through puberty. This insulin resistance, which appears to be related to the puberty-associated rise in growth hormone levels, is exaggerated in teenagers with T1DM, especially adolescents who are overweight or obese [American Diabetes Association. *Diabetes Care* 2006]. There is a need for faster-acting insulins to address the challenges of insulin resistance in the pediatric population. Adolescents with T1DM require large (ie, 0.2–0.3 U/kg) premeal bolus doses of rapid-acting insulin to overcome peripheral resistance in puberty. But, there are negative clinical consequences that are associated with this strategy. They include delayed peak, with early postmeal hyperglycemia, and prolonged duration that suppresses hepatic glucose production, causing late postmeal hypoglycemia, especially after the last meal of the day (Figure 1).

The timely delivery of insulin in doses that match the increase in blood glucose after and between meals is a therapeutic challenge [Stote R et al. *J Diabetes Sci Technol* 2010]. Rapid-acting insulin analogs offer the possibility of immediate preprandial or even postprandial administration in children and adolescents, who often have unpredictable sleep patterns and eating behaviors [Danne T. *Diabetes Care* 2007].

Figure 1. Dose-Dependent Pharmacodynamics of Regular Insulin.



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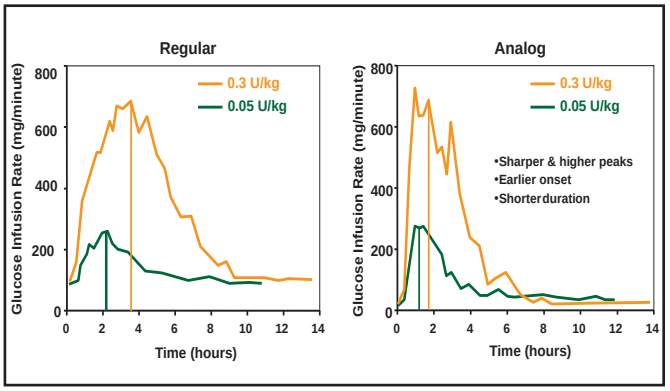
While rapid-acting insulin analogs have a more suitable pharmacokinetic and pharmacodynamic profile than soluble human regular insulin [Heller S et al. *Diabetes Metab Res Rev* 2011], even current insulins work too slowly and last too long for external closed-loop systems—once again resulting in exaggerated postmeal excursions, especially after breakfast, and vulnerability to late postmeal hypoglycemia, particularly after dinner.

More rapidly absorbed insulins can increase bioavailability and achieve greater within-subject consistency of bolus doses (Figure 2). Several approaches are being tested to accelerate the time-action profiles of fast-acting insulins. They include faster insulins; warming of the infusion site; coformulation with hyaluronidase; and alternate routes (microneedle infusion sets, inhaled insulin, and intraperitoneal insulin pumps).

Figure 2. Pharmacodynamics of Regular Versus Rapid-Acting Insulin Analogs.



Reproduced with permission from The American Diabetes Association, [Lys(B28), Pro(B29)]-human insulin. A rapidly absorbed analogue of human insulin. Howey DC et al; vol. 43, 396-402, March 1994.

The present status of these strategies varies. The first and only recombinant human hyaluronidase enzyme,

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 overweightedness (>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 is 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