Of the 450 patients who were on liraglutide, 20% complained of nausea compared with 9% of the 461 patients who were on exenatide. Approximately 13% of patients who were on liraglutide experienced diarrhea compared with 6% of those who were on exenatide. Of patients who were on liraglutide, 11% experienced vomiting compared with 4% of those who were on exenatide. Of those who were on exenatide, 10% had injection-site nodules compared with 1% of those who were receiving liraglutide. There were no major hypoglycemia events in either group, and more than 85% of participants in both treatment arms completed the trial.

Dr. Buse concluded his presentation, pointing out that exenatide once weekly and liraglutide once daily provided effective glucose control, modest weight loss, and infrequent hypoglycemic episodes in patients with uncontrolled T2DM. At the doses that were tested, exenatide once weekly had a moderately smaller reduction in HbA1C (treatment difference at study end 0.2%) and weight (treatment difference at study end 0.9 kg) than liraglutide, administered at the maximum dose, but with less frequent gastrointestinal adverse effects. These differences, along with frequency and method of injection, could be used by clinicians in shared decision-making regarding treatment of patients with type 2 diabetes who are uncontrolled on oral antihyperglycemic agents.

Efficacy of a Bihormonal Closed-Loop System to Control Postprandial and Post Exercise Glucose Excursions

Written by Maria Vinall

Closed-loop systems consist of a continuous glucose sensor that is connected to a computer that contains a glucose control algorithm and this algorithm advises the rate of the insulin pump. Arianne van Bon, MD, Academic Medical Center, Amsterdam, The Netherlands, presented data comparing a bihormonal closed-loop system to control postprandial and post exercise glucose with an open-loop system (usual care, insulin dosing performed by the patient). Overall, the bihormonal closed-loop system (automated glucagon plus insulin delivery) successfully controlled the glucose values in type 1 diabetic patients.

The first prototype, (APPEL 1) was a pilot study that evaluated the feasibility of the bihormonal closed-loop system in 6 subjects with type 1 diabetes postprandially. The closed-loop consisted of subcutaneous continuous glucose monitor (CGM) based on microdialysis, self-learning proportional derivative algorithm built in a personal computer and two D-Tron+ pumps for subcutaneous insulin and glucagon administration [van Bon A et al. *J Diabetes Sci Techno* 2010].

The algorithm had three operating ranges: 1) administer insulin if the glucose level was >7 mmol/L; 2) add glucagon if the glucose level was <3.2 mmol/L; 3) issue an eating alert for glucose levels <5 mmol/L).

One subject was excluded due to technical failure of the CGM. Overall mean venous glucose values were similar between the two systems (open-loop 11.4 mmol/L [5.2 to 14.7]; closed-loop in 8.7 mmol/L [7.1 to 8.8]). There was an initial postprandial rise in glucose with the closed-loop system followed by a drop in glucose values to <5mmol/L. There were four hypoglycemic events (glucose <3.9 mmol/L) in the closed-loop group compared with one event in the open-loop group. These results showed that the technique was feasible, but adjustments were needed.

In the follow-up study (APPEL 2) adjustments were made: a needle type CGM was used instead of microdialysis CGM; two CGMs (one primary and one back up sensor) were used and there was a change in the algorithm. Insulin was administered if glucose levels >6.5 mmol/L, glucagon was given at glucose levels <6.5 mmol/L, and eating alerts were issued when glucose levels were <3.5mmol/L. Rescue glucagon bolus was given when glucose was <4.5 mmol/L. Also, exercise (30 minutes on a home trainer) was introduced to increase stress on the system. Included were 10 patients (8 men and 2 women, mean age 55.4 years) with type 1 diabetes treated with an insulin pump. Subjects had a mean HbA1C of 8.0%, mean duration of diabetes of 34.6 years, and mean pump use of 11.2 years. The glucose was controlled 2 hours after breakfast, during and one and a half hour post exercise, and four hours after lunch.

There were no overall differences in venous and sensor glucose concentrations between the closed-loop system and usual care (open-loop; Table 1). Significantly higher venous glucose levels (p=0.001) were noted in the closed-loop system post exercise. Significantly higher postprandial breakfast (p=0.001) and significantly lower post exercise (p=0.01) glucose concentrations (AUC) were noted in the closed-loop system. The postprandial lunch glucose control was not different. There were no incidents of severe hypoglycemia. Glucose levels <3.5 mmol/L were observed in two patients in the open-loop system and four in the closed-loop system. All patients were given glucagon. In conclusion, the closed-loop system was efficient particularly after lunch when all glucose levels were <6.5 mmol/L suggesting that the glucose level before the meal influences the performance of the algorithm.

Table 1. APPEL 2: Results.

Venous glucose concentrations (mmol/L)	Open-loop	Closed-loop	p value
Overall	9.0	8.7	0.74
Postprandial breakfast	9.5	8.2	0.36
Post exercise	7.5	11.4	0.001
Postprandial lunch	9.4	11.7	0.15
Sensor glucose concentrations	**Open-loop**	**Closed-loop**	**p value**
Overall	0.32	1.6	0.24
Postprandial breakfast	1.6	4.5	0.001
Post exercise	-2.2	-4.8	0.01
Postprandial lunch	2.6	1.5	0.22

Combined Intensive BP and Glycemic Control Has No Benefit in Reducing CV Risk in Patients with T2DM

Written by Rita Buckley

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was a randomized, multicenter clinical trial [NCT00000620] that was conducted in 77 clinical sites in the United States and Canada. The objective of the study was to independently test the impact of three medical strategies to reduce cardiovascular disease (CVD) complications and microvascular complications in type 2 diabetes (T2DM) patients with high cardiovascular (CV) risk (intensive vs standard blood pressure [BP] and/or glycemic control, or statin alone vs statin + fenofibrate). Patrick J. O'Connor, MD, Health Partners Research Foundation, Minneapolis, Minnesota, USA, reported that none of the ACCORD prespecified microvascular outcomes was significantly reduced in participants who were intensively treated for both glycemia and BP compared with those who were treated with either regimen alone, signifying the lack of an additional beneficial effect from combined intensive treatment.

Dr. O'Connor presented data for 4733 patients (mean age 62 years, mean baseline BP 139/76 mm Hg, mean baseline HbA1C 8.3%) who received either standard (goal <140 mm Hg) or intensive (goal <120 mm Hg) BP or standard (HbA1C 7.0% to 7.9%) or intensive (HbA1C <6%) glycemic therapy. Participants were required to have stable T2DM for more than 3 months, HbA1C 7.5% to 11%, and high CV risk (clinical or subclinical disease or ≥2 risk factors). Eligibility also included those aged <80 years with a systolic BP 130 to 160 mm Hg (with 0 to 3 medications), 161 to 170 mm Hg (with 0 to 2 medications), or 171 to 180 mm Hg (with 0 to 1 medication); urine protein <1.0 gm/24 hrs or equivalent; and serum creatinine ≤1.5 mg/dL.

The primary composite outcome was the development of renal failure, or retinal photocoagulation or vitrectomy to treat retinopathy. Other outcomes included nephropathy (development of incident micro- or macroalbuminuria or renal failure), diabetic eye complications (retinal photocoagulation or vitrectomy to treat retinopathy; eye surgery for cataract extraction; or 3-line decrease in visual acuity), neuropathy (score of >2.0 on the Michigan Neuropathy Screening Instrument, loss of vibratory sensation, or loss of light touch).

Over a mean follow-up period of 4.7 years, the primary microvascular composite outcome occurred in 527 of 4733 subjects, including 11.4% of subjects in the intensive BP group and 10.9% in the standard BP arm (HR, 1.08; 95% CI, 0.91 to 1.28). There was no significant difference between patients who received standard versus intensive BP intervention. Of the 9 outcome measures, only the development of microalbuminuria was significantly (HR, 0.84; p=0.02) impacted by treatment (intensive arm 20.8% vs 25.0% for standard arm).

For the primary microvascular composite in the glycemic arms, there was no significant difference between patients who received standard versus intensive therapies. Of the 9 outcome measures, 3 were significantly impacted by treatment (Table 1). There were no significant interactions between the intensive BP and glycemia interventions.

Table 1. Significantly Impacted Outcome Measures.

Outcome Measure	Intensive Arm	Standard Arm	Hazard Ratio	p value
Development of macroalbuminuria	5.3%	7.6%	0.68	0.002
Loss of vibratory sensation	42.4%	46.9%	0.89	0.02
Loss of pressure sensation	11.5%	14.9%	0.76	0.001

Triple Therapy with Liraglutide + Metformin + Insulin Detemir Improves Glycemic Control With No Weight Gain and Low Rates of Hypoglycemia

Written by Maria Vinall

Although metformin is the established first-line treatment option for type 2 diabetes mellitus (T2DM), there is no general consensus regarding which treatment to use