Obesity

GLP-1 mimetic therapy for diabesity: Liraglutide flexes its muscles

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There have been many false dawns in the pharmacological management of type 2 diabetes. While intensive insulin treatment and thiazolidinediones contribute to effective glycaemic control for some people, weight gain is often a problem, and this has rested uneasily with the fact that most people with type 2 diabetes are already obese and hardly welcome further weight gain.

Receptor agonists and analogues of glucagon-like peptide-1 (GLP-1), the new kids on the block, look increasingly to be a significant advance in the treatment of the many obese people with type 2 diabetes.

Exenatide, the first GLP-1 receptor agonist to be licensed, is a naturally occurring peptide produced by the Gila monster. It is administered twice a day by subcutaneous injection. The drug produces significant improvements in glycaemic control similar to those obtained with insulin, but without the weight gain, in people with type 2 diabetes already treated with oral antidiabetes drugs (OADs) (Nauck et al, 2007). This is a particularly good combination of properties, and has led to the inclusion of exenatide in consensus guidelines (Nathan et al, 2009) and NICE guidance (National Collaborating Centre for Chronic Conditions, 2009).

There has been concern about the risks of pancreatitis and allergy in people treated with exenatide, but as with all new drugs it will take time for the full profile of adverse events to emerge.

Liraglutide is the second GLP-1 receptor agonist (and first human analogue) to reach market, and is licensed for use in combination with OADs to treat type 2 diabetes. Apart from the considerable appeal of once-daily administration, it has been uncertain what this currently more expensive drug might have to offer over and above exenatide.

Buse and colleagues (summarised alongside) report on LEAD-6, a randomised, controlled, open-label trial of liraglutide versus exenatide in obese people with type 2 diabetes above glycaemic target despite treatment with OADs. The LEAD-6 study suggests that liraglutide was modestly, but significantly, more effective at lowering blood glucose and body weight than exenatide, and was better tolerated in terms of nausea and hypoglycaemia.

The reasons for these differences are not clear. However, intolerance of exenatide is a significant problem in clinical practice. Any advance that retains or further enhances the efficacy of GLP-1 mimetic therapy in the treatment of overweight and obese people with type 2 diabetes, while minimising the principal adverse effects of nausea and hypoglycaemia, is to be welcomed. These data suggest that liraglutide offers significant advantages over exenatide and is an important treatment advance for those with obesity and type 2 diabetes.

Nathan DM, Buse JB, Davidson MB et al (2009) Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* **52**: 17–30

National Collaborating Centre for Chronic Conditions (2009) *Type 2 Diabetes: The Management of Type 2 Diabetes. NICE Clinical Guideline 87.* NICE, London. Available at: http://tinyurl.com/mzt23a (accessed 09.11.09)

Nauck MA, Duran S, Kim D et al (2007) A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia* **50**: 259–67

LANCET

LEAD-6: liraglutide versus exenatide

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 This 26-week, randomised, parallel-group, multinational, open-label trial compared efficacy and safety of liraglutide with exenatide.

2 Participants with type 2 diabetes were randomly assigned to receive liraglutide 1.8 mg once-daily (n=233) or exenatide 10 µg twice-daily (n=231) in addition to the maximally tolerated dose of metformin or sulphonylurea or both.

3 The primary outcome measure was change in HbA_{1c} level and an intention-to-treat method was used to analyse efficacy.

4 The study population had a mean baseline HbA_{1c} level of 8.2% (66 mmol/mol). HbA_{1c} reductions were significantly larger in those treated with liraglutide than with exenatide (–1.12% [12.2 mmol/mol] vs. –0.79% [8.6 mmol/mol]; P<0.0001).

5 More participants achieved an HbA_{1c} level of less than 7% (<53 mmol/mol) with liraglutide than exenatide (54% vs. 43%; P=0.0015).

6 Weight loss was similar with liraglutide and exenatide (–3.24 kg vs. –2.87 kg, respectively). Both were well-tolerated but minor hypoglycaemia was less frequent (P=0.0131) and nausea less persistent (P<0.0001) in the liraglutide group.

7 Once-daily liraglutide resulted in significantly greater improvements in glycaemic control than twice-daily exenatide. The authors concluded that liraglutide could be a useful treatment for hyperglycaemia in type 2 diabetes, particularly when weight gain and hypoglycaemia are a concern.

Buse J, Rosenstock J, Sesti G et al (2009) Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* **374**: 39–47

PEDIATRIC DIABETES

Weight gain soon after T1D diagnosis

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 This study examined weight change in children with type 1 diabetes (T1D) from the point of diagnosis (Dx) and throughout the first few months post-Dx. Data on 136 children diagnosed between 1991 and 2001 were reviewed.

2 Average age at Dx was 9.02 years (SD 4.46 years) and average HbA_{1c} level was 11.5% (102 mmol/mol).

3 Average BMI z-score at Dx was –0.28 (39th percentile): 13.5% of children had BMI >85th percentile and 7.2% were obese.

4 By 15–41 days post-Dx, mean weight gain was 12.8% and BMI gain 11.9%. Coinciding with an improvement in glycaemic control, a plateau in BMI z-score was observed by week 10. By 71–139 days post-Dx, 31.7% had a BMI ≥85th percentile and 15.9% were obese.

5 By 10–12 weeks post-Dx, almost one third of children were overweight or obese. The authors suggest that closer attention be paid to the overall calorific intake of children with new-onset T1D.

Newfield RS, Cohen D, Capparelli EV, Shragg P (2009) Rapid weight gain in children soon after diagnosis of type 1 diabetes: is there room for concern? *Pediatr Diabetes* **10**: 310–15

PEDIATRICS

HbA_{1c} and FBG: good predictors of diabetes

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Effective screening tools to identify type 2 diabetes (T2D) in children would enable early intervention.

2 HbA_{1c}, 1,5-anhydroglucitrol, fasting blood glucose (FBG) and Homeostasis Model of Assessment for Insulin Resistance [HOMA-IR]) were compared for their effectiveness as potential screening tools for impaired glucose tolerance (IGT) and T2D in obese insulin-resistant obese children.

3 A total of 468 obese children underwent laboratory tests. Of the whole study group, nine participants had T2D and 44 had IGT.

4 Optimal sensitivity and specificity to detect T2D were, respectively, 86% and 85% at HbA_{1c} levels of 5.7% [39 mmol/mol], 88% and 93% at an FBG level of 104 mg/dL, and 62% and 70% at an HOMA-IR of 7.9.

5 HbA_{1c} level, 1,5-anhydroglucitrol and FBG were good predictors of T2D in obese children, whereas HOMA-IR values were not. HbA_{1c} level and 1,5-anhydroglucitrol were excellent predictors of T2D in insulin-resistant obese children.

Shah S, Kublaoui B, Oden J, White P (2009) Screening for type 2 diabetes in obese youth. *Pediatrics* **124**: 573–9

DIABETES CARE

Obstructive sleep apnoea in T2D

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 In this study the prevalence, risk factors and severity of obstructive sleep apnoea (OSA) were assessed in 306 obese people with type 2 diabetes.

2 OSA was measured with home unattended overnight polysomnograpy.

3 Participants were categorised by apnoea-hypopnoea index (AHI) into mild, moderate or severe. More than 86% of participants had OSA with an AHI of ≥5 events per hour. Mean AHI was 20.5±16.8 events/hour; 22.6% had severe OSA (AHI ≥30 events/hour) and 30.5% had moderate OSA (AHI ≤15 and <30 events/hour).

4 Waist circumference correlated significantly with the presence of OSA (odds ratio [OR] 1.1; 95% confidence interval [CI] 1.0–1.1; P=0.03) and severe OSA was found more often in those with a higher BMI (OR 1.1; 95% CI 1.0–1.2; P=0.03).

5 The authors concluded that physicians need to look out for OSA in obese people with type 2 diabetes, especially in those with a higher BMI and waist circumference.

Foster G, Sanders M, Millman R et al (2009) Obstructive sleep apnea among obese patients with type 2 diabetes. *Diabetes Care* **32**: 1017–19

"Physicians need to look out for obstructive sleep apnoea in obese people with type 2 diabetes, especially in those with a higher BMI and waist circumference."

DIABETES

Lifestyle linked with predisposition to hyperglycaemia

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓✓

1 Genetic research has recently discovered and confirmed multiple risk factors for type 2 diabetes (T2D).

2 Gene x physical activity interactions were assessed for 17 polymorphisms in a cohort of middle-aged adults, initially without diabetes.

3 Outcomes were impaired glucose regulation (IGR) versus normal glucose regulation (n=16003), glucose intolerance (n=8860), or incident T2D (n=2063 events).

4 Gene x physical activity interactions on IGR risk for three of the 17 polymorphisms were significant: *CDKN2A/B* rs1081161 ($P_{interaction}$=0.015), HNF1B rs4430796 ($P_{interaction}$=0.026), and PPARG rs1801282 ($P_{interaction}$=0.04).

5 Only one statistically significant interaction was observed where T2D was the outcome: HNF1B rs4430796 variant ($P_{interaction}$=0.0004).

6 The authors concluded that genetic predisposition to hyperglycaemia is partially dependent on lifestyle.

Brito EC, Lyssenko V, Renström F et al (2009) Previously associated type 2 diabetes variants may interact with physical activity to modify the risk of impaired glucose regulation and type 2 diabetes: a study of 16,003 Swedish adults. *Diabetes* **58**: 1411–18