An increase in therapeutic options for type 2 diabetes

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The therapeutic environment in terms of glucose-lowering therapies for type 2 diabetes is already crowded. We have biguanides (well, metformin anyway), sulphonylureas, meglitinides, α-glucosidase inhibitors, thiazolidinediones and, of course, insulin. The extension to the license for pioglitazone to include triple therapy and co-prescription with insulin increases the permutations further. The incretin hormone glucagon-like peptide 1 (GLP-1) and other agents that inhibit the metabolism of dipeptidyl peptidase IV (DPP-IV) inhibitors expand the possible choices further. The paper from Nauck et al (summarised to the right) cautiously and modestly introduces the incretin mimetic class of antidiabetic agents to the therapeutic arena in a non-inferiority study.

Exenatide, the first-in-class incretin mimetic, shares several glucoregulatory actions with GLP-1. The GLP-1 mimetics act to correct key defects in the enteroinsular axis that commonly accompany and may be important in the pathogenesis of type 2 diabetes. The outcomes include enhanced glucose-dependent insulin secretion, suppression of post-prandial glucagon secretion, a feeling of satiety and a slowing of gastric emptying.

Nauck et al's study was designed to compare the safety and efficacy of exenatide with biphasic insulin aspart 30/70 in people with type 2 diabetes failing to reach optimal treatment goals with a combination of metformin and sulphonylurea. Participants were generally overweight or obese (average BMI: 30.4 kg/m^2) with a long duration of diabetes (mean: 10 years) and sub-optimal glucose control (mean HbA_{1c}: 8.6 %). A total of 253 patients were randomised to exenatide and 248 to insulin aspart 30/70. By study end, 54 (21 %) people using exenatide had withdrawn compared with 25 out of 248 taking insulin (10.1 %), mostly due to gastrointestinal adverse events. Of those who continued exenatide treatment 80 % were using the 10 µg twice-daily dose, whereas the mean insulin dose increased from 15.7 ± 9.5 units per day to 24.4 ± 15.6 units per day. Insulin doses were adjusted to optimise control and minimise hypoglycaemia. The simple dose titration, the low risk for hypoglycaemia (though care and possibly dose reduction of sulphonylurea therapy is required) and the progressive weight loss associated with exenatide, in contrast to the progressive weight gain which bedevils insulin, are, on the face of it, major potential benefits of exenatide.

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It's great to see simple, relevant, valid, well-conducted trials like this present agents such as exenatide carefully without the razzmatazz of inflated claims but with encouragement that it currently looks as good as, and maybe significantly better than, currently available add-on therapies. It is likely to meaningfully extend choice and usefully increase the therapeutic options for type 2 diabetes.

DIABETOLOGIA

Safety and efficacy of exenatide

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

1 This study aimed to assess the safety and efficacy of the incretin mimetic exenatide compared with biphasic insulin aspart 30/70.

2 People with diabetes receiving metformin plus sulphonylurea treatment were randomised to either exenatide (5 µg twice daily for 4 weeks; 10 µg thereafter) or twice-daily doses of biphasic insulin aspart 30/70 (253 and 248 participants, respectively).

3 Exenatide achieved glycaemic control similar to biphasic insulin aspart, and fasting serum glucose was significantly reduced with both treatments (exenatide: 1.8 ± 0.2 mmol/l; $P < 0.001$; biphasic insulin aspart: 1.7 ± 0.2 mmol/l; $P < 0.001$).

4 Weight loss was observed in people using exenatide, whereas biphasic insulin aspart 30/70 resulted in a weight increase.

5 Exenatide led to greater postprandial glucose excursion reductions following morning ($P < 0.001$), midday ($P = 0.002$) and evening ($P < 0.001$) meals.

6 Withdrawal rates for exenatide and biphasic insulin aspart were 21.3 % and 10.1 %, respectively, and the most common side effect of exenatide was nausea, which had an incidence of 33 %.

7 The authors conclude that exenatide is a potential alternative treatment for type 2 diabetes owing to its better postprandial glucose control, although the implications of the associated weight reduction are yet to be defined.

8 Biphasic insulin aspart 30/70 is also a promising treatment owing to a lower risk of adverse gastrointestinal events.

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

DIABETIC MEDICINE

Impaired fasting glucose and type 2 diabetes incidence

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

1 This study investigated how the incidence of type 2 diabetes is linked to different cut-off points for impaired fasting glucose (IFG).

2 Between 1990 and 2000, 1040 adults without diabetes (40–49 years of age) were assessed using clinical, anthropometric and biochemical measurements, and an oral glucose tolerance test.

3 A 10-year cumulative incidence of diabetes was reported as 7.3 per 1000 person years.

4 In those people classified as normoglycaemic (<5.6 mmol/l) cumulative incidence of diabetes was 2.4 per 1000 person years. In people with an IFG classified as lower range (5.6–6.0 mmol/l) incidence was 6.2 per 1000 person years; and in those with the standard ADA definition of IFG (6.1–6.9 mmol/l) it was 17.5.

5 The age/sex-adjusted risk for incident diabetes increased in the lower IFG category compared with normoglycaemia; however, the greatest difference in risk was in the IFG-original group (HR: 6.9; CI: 3.1, 15.2).

6 The incidence of diabetes is associated more strongly with the IFG-original values than the lower IFG-score and full-range (5.6–6.9 mmol/l) categories.

7 When considering diabetes risk in terms of IFG, this study recommends the use of a 6.1 mmol/l cut-off point.

Forouhi NG, Luan J, Hennings S, Wareham NJ (2007) Incidence of Type 2 diabetes in England and its association with baseline impaired fasting glucose: the Ely study 1990-2000. *Diabetic Medicine* **24**: 200–7

DIABETES AND METABOLISM

Intensive multi-therapy improves QOL

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

1 Quality of life (QOL), attitudes, self-management and knowledge in people with type 2 diabetes following intensive multi-therapy (IMT) were investigated in this 12-month RCT.

2 IMT included monthly clinical and biochemical assessment, diet education, exercise, medical diabetes management and medication adjustments, while the control group received conventional treatment from their physician.

3 A validated, diabetes-specific questionnaire was developed and administered at 0, 6 and 12 months.

4 IMT improved QOL scores significantly at 12 months compared with the control group ($P < 0.001$). Knowledge and self management scores also improved significantly ($P<0.047$ and <0.001, respectively).

Menard J, Payette H, Dubuc N et al (2007) Quality of life in type 2 diabetes patients under intensive multitherapy. *Diabetes and Metabolism* **33**: 54–60

DIABETES AND METABOLISM

Maternal history of diabetes linked to diabetic nephropathy

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

1 This study investigated the impact of parental history of type 2 diabetes on diabetic nephropathy in type 1 offspring.

2 Information on cardiovascular disease and family history was obtained from 160 people with type 1 diabetes.

3 Compared with people with no parental history of diabetes, insulin resistance and renal complications were most common in people with a maternal history of type 2 diabetes ($P=0.043$ and 0.0041, respectively).

4 The time to development of abnormal albuminuria was also significantly less for individuals with a maternal history of type 2 diabetes or a familial history of premature cardiovascular disease.

5 In a controlled analysis, maternal history independently predicted diabetic nephropathy in type 1 diabetes.

6 This suggests that imprinted genes might predispose people to diabetic renal disease.

Hadjadj S, Duengler F, Torremocha F et al (2007) Maternal history of type 2 diabetes is associated with diabetic nephropathy in type 1 diabetic patients. *Diabetes and Metabolism* **33**: 37–43

CIRCULATION

Clopidogrel dose and platelet inhibition

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

1 The authors of this study investigated whether clopidogrel treatment reduces platelet inhibition in people with type 2 diabetes on chronic dual antiplatelet therapy.

2 People with type 2 diabetes who had a suboptimal response to clopidogrel were randomised to receive either a 75 or 150 mg daily maintenance dose of the drug (n=20 per group).

3 Platelet function was measured at baseline, 30 days after randomisation and 30 days after resuming standard dosing.

4 Compared with the lower dose, the 150 mg group resulted in significantly reduced maximal adenosine diphosphate-induced platelet aggregation ($P=0.002$), although suboptimal clopidogrel response was still observed in 60% of the high-dose group.

5 The results show that platelet effects are enhanced by a 150 mg dose of clopidogrel compared with 75 mg in those with type 2 diabetes. Future large-scale clinical trials should asses the implications of ex vivo platelet reactivity.

Angiolillo DJ, Shoemaker SB, Desai B et al (2007) Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study. *Circulation* **115**: 708–16

'Imprinted genes might predispose people to diabetic renal disease.'

'Platelet effects are enhanced by a 150 mg dose of clopidogrel compared with 75 mg.'

'Pioglitazone can lead to metabolic and histological improvements.'

NEW ENGLAND JOURNAL OF MEDICINE

Pioglitazone benefits in nonalcoholic steatohepatitis

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

1 It was hypothesised that some symptoms of nonalcoholic steatohepatitis (characterised by insulin resistance, steanosis and necroinflammation with or without centrilobular fibrosis) could be reversed with administration of a thiazolidinedione.

2 The study population consisted of people with impaired glucose tolerance or type 2 diabetes who also had nonalcoholic steatohepatitis confirmed by a liver biopsy.

3 Participants were assigned either a hypocaloric diet of 500 kcal per day less than that required to maintain body weight plus 45 mg pioglitazone daily (n=26), or a hypocaloric diet plus placebo (n=21).

4 Compared with diet plus placebo, diet plus daily pioglitazone significantly improved glycaemic control and glucose tolerance after 6 months ($P<0.001$).

5 Also significantly decreased by the diet plus pioglitazone treatment when compared with placebo were plasma aspartate aminotransferase levels ($P=0.04$), alanine aminotransferase levels ($P<0.001$) and hepatic fat content ($P<0.001$). Hepatic fat insulin sensitivity increased significantly ($P=0.008$) versus placebo.

6 When compared with the control group, those receiving pioglitazone showed significant improvements in histological factors and necroinflamation. Reductions in the levels of fibrosis did not vary significantly ($P=0.08$).

7 The results of this trial suggest that pioglitazone can lead to metabolic and histological improvements in this patient group.

Belfort R, Harrison SA, Brown K et al (2006) A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *New England Journal of Medicine* **355**: 2297–307

'The presence and number of diabetes complications is related to the degree of cortisol secretion in type 2 diabetes.'

DIABETES CARE

Gestational diabetes and body fat increase risk of IGT

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

1 This study assessed Korean women with previous gestational diabetes, which is associated with the future development of type 2 diabetes.

2 Women with previous gestational diabetes and impaired glucose tolerance (IGT; n=21) were identified using a 75 g oral glucose tolerance test. They were compared with 60 age- and BMI-matched women with previous gestational diabetes and normal glucose tolerance and 18 women with no history of diabetes and normal glucose metabolism during pregnancy.

3 Tetrapodal bioelectrical impedance measured total body fat and a single cut of a computed tomography scan determined visceral fat. Insulin sensitivity was measured with the intravenous glucose tolerance test.

4 Visceral fat was greatest in women with IGT at 1 year postpartum, suggesting that in women with recorded gestational diabetes visceral obesity is a possible pathophysiological mechanism for the development of impaired glucose metabolism. These women also had lower insulin response to glucose and lower β-cell function.

5 The authors conclude that high body fat content (especially visceral fat) and a low insulin sensitivity index are risk factors in the development of impaired glucose metabolism in Korean women with previous gestational diabetes.

Lim S, Choi SH, Park YJ et al (2007) Visceral fatness and insulin sensitivity in women with a previous history of gestational diabetes mellitus. *Diabetes Care* **30**: 348–53.

DIABETES CARE

Cortisol secretion is enhanced in people with type 2 diabetes

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

1 The aim of this study was to investigate the relationship between type 2 diabetes and enhanced cortisol secretion.

2 Cortisol secretion was measured in 170 people with type 2 diabetes and 71 controls matched for age, sex and BMI.

3 Adrenocorticotropic hormone levels were assessed at 08:00 and serum cortisol levels at 12:00 then at 09:00 following a 1 mg overnight dexamethasone suppression test. In addition, 24-hour urinary-free cortisol (UFC) was measured.

4 Chronic complications were recorded and further used to categorise participants: as presenting complications (n=117) or not (n=53).

5 UFC was higher in people with diabetes who had complications (125.2±4.6 nmol/24 h) than those without (109.2±6.8 nmol/24 h; $P=0.057$) and versus the control group (101.7±5.9 nmol/24 h; $P=0.002$).

6 Serum cortisol levels at 12:00 pm were also higher in the group with complications than the group without (120.6±4.1 versus 99.7±6.1; $P=0.005$) and higher than the control group (120.6±4.1 versus 100.3±5.3 nmol/l; $P=0.003$).

7 Logistic regression demonstrated that diabetes complications were significantly associated with serum cortisol levels at 12:00 ($P<0.0001$), diabetes duration ($P<0.0001$), sex ($P<0.041$) and HbA_{1c} ($P<0.044$).

8 The authors concluded that the presence and number of diabetes complications is related to the degree of cortisol secretion in type 2 diabetes.

Chiodini I, Adda G, Scillitani A et al (2007) Cortisol secretion in patients with type 2 diabetes: relationship with chronic complications. *Diabetes Care* **30**: 83–8