A new tool to help in the diagnosis of diabetes

Daniel Flanagan, Consultant Physician, Derriford Hospital, Plymouth

It is clear that raised blood glucose is not a diagnosis in itself, but it is the manifestation of a number of disease processes. This group of conditions has been labelled diabetes mellitus and until recently, for the majority of people, this classification was adequate.

Very simply, raised blood glucose is either a consequence of an insulin secretion problem or a problem with resistance to the actions of insulin. For most people with diabetes the defect is ill-defined. In type 1 diabetes, one or more triggers causes rapid loss of insulin secretion and perhaps, to some extent, pre-existing insulin resistance may exacerbate this. For individuals with type 2 diabetes, the exact roles of insulin resistance and deficient insulin secretion are less clear.

It is now possible to define the specific problem in groups of individuals with monogenic diabetes as well as a variety of other endocrine conditions that may result in raised blood glucose. These specific forms of diabetes may require specific therapies and are likely to have differing prognoses. There has also been a rapid proliferation in the available treatments for diabetes. These are focused on targeting insulin resistance or insulin secretion defects. It is becoming increasingly important to make an accurate diagnosis on an individual basis.

In order to identify these disease processes it is important to accurately define endogenous insulin secretion. The established measure has been serum C-peptide levels in response to a standardised mixed meal tolerance test. Unfortunately C-peptide rapidly degrades in blood and needs to be analysed or frozen immediately after sampling, which limits its use.

The article from Besser et al (2011; summarised alongside) describes the development of a urine-based measure of C-peptide. This appears to be stable over a number of days and holds the promise of a much simpler outpatient measure of insulin secretion. This has much wider implications than just identifying small sub-groups with monogenic diabetes. There is the potential to define more precisely groups of people who may benefit from specific therapies. For example, we currently use thiazolidinediones to manage insulin resistance without any measure of whether individuals are still able to mount an insulin response.

Similarly, the glucagon-like peptide-1 receptor agonists hold great promise but being able to define which people have enough endogenous insulin reserve to benefit from treatment would be enormously valuable. The continuing debate over the place of insulin therapy in type 2 diabetes can only be progressed if we have some measure of whether the individual has high or low endogenous insulin production.

It is early days for what appears to be a promising test. If it proves robust then there is the potential for a great impact on clinical care.

DIABETES

"Legacy effect" for atherosclerosis

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

1 The long-term effects of intensive diabetes treatment on atherosclerosis were analysed in this study, which looked at data from 1116 participants of the EDIC (Epidemiology of Diabetes Interventions and Complications) trial.

2 Common carotid intima-media thickness was measured and progression of this measure of atherosclerosis from years 1–6 was 0.019 mm less in the intensive group than in the control group ($P<0.0001$).

3 It was found that intensive diabetes treatment slowed atherosclerosis progression for up to 6 years but not in the years following (6–12 years).

Polak JF, Backlund JY, Cleary PA et al (2011) Progression of carotid artery intima-media thickness during 12 years in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. *Diabetes* **60**: 607–13

DIABETES CARE

Urine C-peptide creatinine ratio is a sensitive and specific method

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

1 The gold standard measure of endogenous insulin secretion is stimulated serum C-peptide during a mixed meal tolerance test (MMTT), but practical issues restrict its use to the hospital setting.

2 This study assessed urine C-peptide creatinine ratio (UCPCR) as an alternative and more practical test.

3 A total of 72 people with type 1 diabetes (median age at diagnosis, 14 years [interquartile range, 10–22]; diabetes duration, 6.5 years [interquartile range, 2.3–32.7]) took part in the study.

4 Participants had an MMTT and stimulated serum C-peptide was collected at 90 minutes. Urine for UCPCR was collected at 120 minutes and following a home evening meal.

5 Both the 120-minute UCPCR and the 120-minute postprandial evening meal UCPCR were highly correlated to the 90-minute serum C-peptide test results ($r=0.97$ [$P<0.0001$] and $r=0.91$ [$P<0.0001$], respectively).

6 A UCPCR ≥0.53 nmol/mmol had 94% sensitivity and 100% specificity for significant endogenous insulin secretion (90-minute serum C-peptide ≥0.2 nmol/L) and a UCPCR of ≥0.37 nmol/mmol had 84% sensitivity and 97% specificity for a serum C-peptide ≥0.2 nmol/L.

7 UCPCR was concluded to be a sensitive and specific method for detecting insulin secretion and may be more practical than serum C-peptide.

Besser RE, Ludvigsson J, Jones AG et al (2011) Urine C-peptide creatinine ratio is a noninvasive alternative to the mixed-meal tolerance test in children and adults with type 1 diabetes. *Diabetes Care* **34**: 607–9

"In children and adults with T1D, use of real-time continuous glucose monitoring was associated with less time in hypoglycaemia and improved HbA_{1c} level."

DIABETES CARE

Closed-loop algorithm performs well overnight at early and late stages of pregnancy

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

1 Closed-loop insulin delivery using a model predictive control (MPC) algorithm was evaluated in pregnant women with T1D in early (12–16 weeks) compared with late (28–32 weeks) gestation.

2 Ten women with T1D were studied over a 24-hour period at early and late gestation (mean age of participants, 31 years; mean diabetes duration, 19 years; mean BMI, 24.1 kg/m^2; mean HbA_{1c}, 6.9% (52 mmol/mol).

3 Continuous glucose monitoring data were fed into the MPC algorithm every 15 minutes and a nurse adjusted the basal insulin infusion rate.

4 Median plasma glucose levels during closed-loop insulin delivery were 6.5 mmol/L in early and 7.0 mmol/L in late gestation (P=0.72).

5 Overnight, the mean plasma glucose time in target (interquartile range, 3.5–7.8 mmol/L) was 84% (50–100%) in early and 100% (94–100%) in late pregnancy (P=0.09).

6 The overnight mean time spent in hyperglycaemia (>7.8 mmol/L) was 7% (0–40%) in early and 0% (0–6%) in late pregnancy, and in hypoglycaemia (<3.5 mmol/L) was 0% (0–3%) in early and 0% (0–0%) in late pregnancy (P=0.18).

7 The authors concluded that the performance of the MPC algorithm was maintained throughout pregnancy suggesting that closed-loop insulin delivery could be used safely overnight in pregnant women with T1D.

Murphy HR, Elleri D, Allen JM et al (2011) Closed-loop insulin delivery during pregnancy complicated by type 1 diabetes. *Diabetes Care* **34**: 406–11

DIABETES CARE

Real-time CGM reduced hypos

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

1 This randomised, controlled, multi-centre study assessed the impact of continuous glucose monitoring (CGM) on hypoglycaemia in 120 children and adults with T1D.

2 Participants were randomly assigned to either the control group performing self-monitoring of blood glucose and wearing masked CGM for 5 days every other week, or a group using real-time CGM.

3 The time spent in hypoglycaemia (<3.5 mmol/L) over the study period (26 weeks) was significantly shorter in the CGM group compared with the control group (0.48 and 0.97 hours/day, respectively; P=0.03).

4 HbA_{1c} was lower in the CGM group compared with the control group (P=0.008).

5 In children and adults with T1D, use of real-time CGM was associated with less time in hypoglycaemia and improved HbA_{1c} level.

Battelino T, Phillip M, Bratina N et al (2011) Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care* **34**: 795–800

DIABETES CARE

Insulin degludec well tolerated in phase II trial

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

1 The efficacy and safety of insulin degludec – an ultra-long-acting basal analogue insulin – were assessed in this exploratory phase II trial.

2 A total of 59 participants received insulin degludec 600 µmol/L; 60 received the 900 µmol/L dose and 59 received insulin glargine.

3 Mean HbA_{1c} levels at 16 weeks were comparable across all groups. Insulin degludec 600 µmol/L, 7.8±0.8% (62±8.7 mmol/mol); insulin degludec 900 µmol/L, 8.0±1.0% (64±10.9 mmol/mol); and insulin glargine, 7.6±0.8% (60±8.7 mmol/mol).

4 Estimated mean rates of hypoglycaemia were lower for both doses of insulin degludec compared with insulin glargine.

5 It was concluded that insulin degludec has comparable glycaemic control and less hypoglycaemia than insulin glargine.

Birkeland KI, Home PD, Wendisch U et al (2011) Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. *Diabetes Care* **34**: 661–5

DIABETOLOGIA

Immunosuppression could improve beta-cell function

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

1 This study investigated whether immunosuppression therapy would improve beta-cell function in people with long-standing T1D.

2 Pancreatic beta-cell function was observed in 22 people with T1D who were taking rapamycin in preparation for islet-cell transplantation.

3 There were also 14 control participants awaiting islet-cell transplantation but without rapamycin.

4 Fasting C-peptide levels increased from <0.03 nmol/L at baseline to 0.039 nmol/L at the end of rapamycin monotherapy (P<0.005).

5 Insulin requirements decreased from 0.64 U/kg each day to 0.57 U/kg (P=0.01). This reduction was only significant in the 12 people who had the largest increase in C-peptide level.

6 The authors concluded that immunosupression therapy may improve beta-cell function.

Piemonti L, Maffi P, Monti L et al (2011) Beta cell function during rapamycin monotherapy in long-term type 1 diabetes. *Diabetologia* **54**: 433–9