Changing the paradigm of type 1 diabetes: It is not a disease of absolute insulin deficiency

Daniel Flanagan
Consultant Physician, Derriford Hospital, Plymouth

We are all familiar with the paradigm that type 1 diabetes is a disease of absolute insulin deficiency. We usually explain to people who have recently been diagnosed with diabetes that, although they may have some ability to make insulin around the time of diagnosis, this ability is likely to progressively fail over the following months. Previous studies (based on the older, less sensitive C-peptide assays) have suggested that, by 5 years, the majority of people with type 1 diabetes will have no ability to make endogenous insulin as measured by blood C-peptide concentrations.

There is a small percentage of people who are still able to make small amounts of insulin, but these are the exception rather than the rule. Data from the DCCT (Diabetes Control and Complications Trial) suggest that this ability to make even small amounts confers some protection from the risk of developing microvascular complications and hypoglycaemia.

With the development of more sensitive C-peptide assays, we are starting to see papers documenting very low concentrations of insulin production in the majority of individuals with long-standing diabetes (Wang et al, 2012). Post-mortem reports also show that beta-cells can be identified in the pancreas of individuals with long-standing diabetes (Foulis et al, 1986). What is not known is how this correlates with C-peptide production and whether these beta-cells may be functional.

The paper by Oram and colleagues (summarised alongside) has added to our understanding of this problem. The authors have used the recently developed urinary C-peptide assay – a sensitive and specific measure of endogenous insulin production – in a cohort of people with type 1 diabetes of greater than 5 years' duration. Measuring urinary C-peptide following a mixed meal, the authors have shown that detectable C-peptide is present in 51 out of 74 individuals (69%) with type 1 diabetes. For the first time they have shown that, in 90% of these people, C-peptide increased in response to a meal, suggesting that functional beta-cells are present.

The results will need reproducing; however, this article provides an obvious therapeutic target for the future. We need to understand why and how some functional beta-cells remain before this can influence therapy. ■

Foulis AK, Liddle CN, Farquharson MA et al (1986) The histopathology of the pancreas in type 1 (insulin-dependent) diabetes mellitus: a 25-year review of deaths in patients under 20 years of age in the United Kingdom. *Diabetologia* **29**: 267–74

Wang L, Lovejoy NF, Faustman DL (2012) Persistence of prolonged C-peptide production in type 1 diabetes as measured with an ultrasensitive C-peptide assay. *Diabetes Care* **35**: 465–70

Diabetologia

Beta-cell function in people with T1D: Detecting C-peptide

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 New ultra-sensitive assays have been developed that detect C-peptide levels <5 pmol/L, which can be used to detect small concentrations of C-peptide in people with long-standing T1D. This study aimed to assess the prevalence of low-level C-peptide secretion as a measure of insulin secretion in people with T1D, and to see if this is a response to a meal stimulus.

2 Seventy-four people with T1D for over 5 years underwent a mixed-meal tolerance test; fasting and stimulated serum C-peptide levels were measured. Blood samples were taken 90 minutes after completion of the mixed meal, and urine samples were taken after 120 minutes.

3 C-peptide rose from a median fasting value of 12 pmol/L to 23 pmol/L after the mixed meals were ingested ($P<0.0001$).

4 C-peptide levels >3.3 pmol/L were detected post-meal in 54 out of 74 participants. Of these 54, C-peptide either increased ($n=43$ [90%]) or stayed the same ($n=11$) compared to median fasting value.

5 Most participants (51 of 74 [69%]) also had detectable C-peptide in urine samples (>30 pmol/L).

6 The conclusion of the study was that most people with long-duration T1D continue to secrete very-low-level endogenous insulin, which increases after meals. This may be due to the presence of a small number of still functional beta-cells, or it may imply that some beta-cells escaped immune attack or have undergone regeneration.

Oram RA, Jones AG, Besser RE et al (2014) The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells. *Diabetologia* **57**: 187–91

Diabetes Technol Ther

Improving HbA_{1c} with improved overnight and breakfast glucose levels

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 As part of the STAR (Sensor-Augmented Pump Therapy for A_{1c} Reduction) 3 trial, 196 people with T1D were randomised to receive sensor-augmented pump therapy to measure its effectiveness at glucose control in comparison to multiple daily insulin injections.

2 This sub-analysis investigated the association between continuous glucose monitoring glucose (CGM-glucose) levels at different times of the day with improvement in HbA_{1c} from baseline to 1-year follow-up.

3 The mean CGM-glucose values for each time period represent the mean of values recorded every 5 minutes on each day of CGM use (i.e. daytime [06.00–00.00], overnight [00.00–06.00] and each mealtime).

4 Improvement in HbA_{1c} after 1 year was associated with improvements in mean CGM-glucose levels during the daytime, overnight and for each mealtime period ($P<0.0001$ for each).

5 In multivariable analysis, only improvement in breakfast mealtime CGM-glucose levels was associated with improved HbA_{1c} after 1 year.

6 There was also an associated improvement in breakfast mealtime CGM-glucose among those who only had improved CGM-glucose in the overnight period.

7 Breakfast period CGM-glucose was improved by overnight CGM-glucose, and improving breakfast mealtime CGM-glucose caused the greatest improvement in HbA_{1c}.

Maahs DM, Chase HP, Westfall E et al (2014) The effects of lowering nighttime and breakfast glucose levels with sensor-augmented pump therapy on hemoglobin A1c levels in type 1 diabetes. *Diabetes Technol Ther* 22 Jan [Epub ahead of print]

Diabetes Care

10-second sprint and hypoglycaemia risk

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓

1 The aim of this study was to determine whether a 10-second sprint after 30 minutes of moderate-intensity exercise increases the amount of carbohydrates required and prevents late-onset post-exercise hypoglycaemia (LOPEH) in people with T1D ($n=7$). (A 10-second sprint in hyperinsulinaemic conditions is known to stop the fall in glycaemia during early recovery.)

2 All participants underwent a hyperinsulinaemic-euglycaemic clamp and performed two exercise sessions on separate days, followed either by a sprint at maximal effort or no sprint.

3 The 10-second sprint did not affect the amount of carbohydrate required to maintain glycaemia during 8-hour recovery post-exercise, and it did not reduce the risk of LOPEH.

Davey RJ, Bussau VA, Paramalingam N et al (2013) A 10-s sprint performed after moderate-intensity exercise neither increases nor decreases the glucose requirement to prevent late-onset hypoglycemia in individuals with type 1 diabetes. *Diabetes Care* **36**: 4163–5

Diabetes Care

Ischaemic heart disease mortality

Readability	✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 The study aim was to determine whether ischaemic heart disease (IHD) mortality among people with T1D depends on age at onset and whether this effect is sex specific.

2 Early and late onset were defined as T1D diagnosis at 0–14 years and 15–29 years respectively.

3 Data from a Finnish cohort of 17 306 people were analysed; during 433 782 person-years of follow-up, 478 deaths from IHD occurred.

4 The standardised mortality ratio was higher in women than men (21.6 [95% confidence interval [CI], 17.2–27.0] vs 5.8 [95% CI, 5.1–6.6]). The difference between the sexes was more striking in the early-onset cohort.

5 The increased risk of dying from IHD as a result of T1D is more pronounced in women than men.

6 This underscores the necessity to identify risk factors early in women and treat IHD more aggressively after diagnosis.

Harjutsalo V, Maric-Bilkan C, Forsblom C, Groop PH (2014) Impact of sex and age at onset of diabetes on mortality from ischemic heart disease in patients with type 1 diabetes. *Diabetes Care* **37**: 144–8

Diabetes Care

Chronic fatigue

Readability	✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 This cross-sectional observational study investigated the relationship between T1D and chronic fatigue and aimed to identify any potential determinants of chronic fatigue.

2 In total, 214 people with T1D were age- and sex-matched with controls. They all completed questionnaires, and HbA_{1c} values and medical records were assessed. Sixty-six participants underwent continuous glucose monitoring combined with an electronic fatigue diary for 5 days.

3 People with T1D experienced chronic fatigue more often than controls (40% vs 7% respectively; $P<0.001$).

4 Age, depression, pain, sleeping problems, low self-efficacy concerning fatigue and physical inactivity were factors significantly associated with chronic fatigue. Glucose parameters were not significantly associated with fatigue.

5 Targeting behavioural interventions could be helpful to manage chronic fatigue in people with T1D.

Goedendorp MM, Tack CJ, Steggink E et al (2014) Chronic fatigue in type 1 diabetes: highly prevalent but not explained by hyperglycemia or glucose variability. *Diabetes Care* **37**: 73–80

> *"The increased risk of dying from ischaemic heart disease as a result of T1D is more pronounced in women than men."*