Management of type 1 diabetes

Skin autofluorescence: A new tool to predict diabetes risk?

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Advanced glycation end products, or AGEs, have been talked about for the past 20 years as contributors to the microvascular complications of diabetes. AGEs are a mixture of molecules that are formed by sugars reacting with amino-acids. They form at a slow steady rate in the human body as a function of aging. Their formation is, however, markedly accelerated in people with diabetes by the presence of glucose. The initial stages of AGE formation are reversible – HbA_{1c} is an example of this.

There is strong evidence that AGEs are implicated in the development of almost all diabetes complications and studies link AGE formation to each of the microvascular complications. AGEs also appear to play an important part in the development of atherosclerotic lesions. Until now, the problem has been that to measure AGE required a skin biopsy, making serial measurements difficult. This paper by Sugisawa et al (summarised alongside) is interesting because it offers the potential to measure AGE using an ultraviolet probe on the skin, with the presence of AGEs corresponding to the degree of skin autofluorescence. The authors have studied a group of people with relatively long duration T1D. Skin AGE accumulation was measured using an autofluorescence reader and compared with a cumulative measure of HbA_{1c}. There was a significant relationship between AGE accumulation and previously measured HbA_{1c}. Autofluorescence measures of AGE were also associated with the development of nephropathy and retinopathy. The authors did not compare autofluorescence scores with any direct measures of skin AGE accumulation, although this work has been done by the developers of the device (Meerwaldt et al, 2004).

This paper, together with previous publications, suggests that we can measure AGE repeatedly over time in an individual to assess change. From a research point of view this will help us to study interventions that might prevent long-term complications of diabetes. From a clinical care perspective the potential of this relatively new test might be to target those most at risk of complications and focus individually on risk factor reduction. This non-invasive technique will not replace measurement of HbA_{1c} but may help as another predictor of who is at risk of complications and may allow intervention trying to reduce the impact of AGE production.

Meerwaldt R, Graaff R, Oomen PH et al (2004) Simple non-invasive assessment of advanced glycation endproduct accumulation. *Diabetologia* **47**: 1324–30

DIABET MED

The Somogyi effect: A rare occurrence

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

1 The "Somogyi effect" proposes that asymptomatic nocturnal hypoglycaemia may cause fasting hyperglycaemia via a counter-regulatory hormone release, although evidence for this is much debated.

2 The authors sought to investigate the Somogyi effect by examining the fasting capillary glucose of 89 people with T1D after nights with nocturnal hypoglycaemia (blood glucose <3.5 mmol/L) and after nights without.

3 Lower fasting capillary blood glucose was observed after nights with hypoglycaemia compared to nights without (5.5 [3.0] versus 14.5 [4.5] mmol/L, $P<0.0001$) and was reduced after nights with more episodes of severe nocturnal hypoglycaemia (5.5 [3.0] versus 8.2 [2.3] mmol/L; $P=0.018$).

4 Nocturnal hypoglycaemia occurred in 94% of nights when fasting capillary blood glucose was <5 mmol/L, with only 2 episodes of fasting capillary blood glucose >10 mmol/L following nocturnal hypoglycaemia.

5 The authors concluded that the Somogyi effect rarely occurs.

Choudhary P, Davies C, Emery CJ et al (2013) Do high fasting glucose levels suggest nocturnal hypoglycaemia? The Somogyi effect. *Diabet Med* 18 Mar [Epub ahead of print]

DIABETES CARE

Skin autofluorescence is associated with past glycaemic control

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

1 The detection of advanced glycation end products (AGEs) via skin autofluorescence (AF) has been found to correlate with the extent of diabetic retinopathy and nephropathy in individuals with T1D.

2 In this study, the authors explored the correlation between skin AF, past glycaemic control and microvascular complications in a cohort of Japanese people with T1D.

3 The accumulation of AGEs was measured using an AF reader in a total of 241 participants and compared to 110 controls.

4 Higher AF values were associated with more severe retinopathy ($P<10^{-11}$) and nephropathy ($P<10^{-5}$). Skin AF values were also associated with the stage of renal and retinal disease displayed by participants.

5 HbA_{1c} area under the curve (AUC) values over a period of 20 years were found to correspond with skin AF measurements (past 5 years, $R=0.35$; $P<0.0001$; past 10 years, $R=0.36$; $P<0.0001$; past 15 years, $R=0.55$; $P<0.0001$; past 20 years, $R=0.22$; $P=0.13$). Interestingly, HbA_{1c} AUC measures from the past 3, 5, 10 and 15 years were associated with the extent of nephropathy and retinopathy.

6 The authors concluded that skin AF is significantly correlated with previous glycaemic control and could serve as a clinical marker of microvascular complications in people with T1D.

Sugisawa E, Miura J, Iwamoto Y et al (2013) Skin autofluorescence reflects integration of past long-term glycemic control in patients with type 1 diabetes. *Diabetes Care* 11 Apr [Epub ahead of print]

"The authors concluded that a 25% pre-exercise and 50% post-exercise, rapid-acting insulin dose could protect people with T1D against early, but not late onset hypoglycaemia."

DIABETES CARE

Exercise-induced hypoglycaemia and insulin dose

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

1 Although people with T1D are encouraged to partake in regular exercise, hypoglycaemia can occur as a result of increased physical activity. Previous literature has suggested that reduced doses of pre- or post-exercise, rapid-acting insulin may be effective in lowering the risk of hypoglycaemia.

2 The aim of this study was to examine the short-term and 24-hour glycaemic responses to reductions in post-exercise, rapid-acting insulin dose in a group of 11 people with T1D.

3 Over 3 mornings, participants were given a 25% dose of rapid-acting insulin before performing 45 minutes of treadmill running (72.5 ± 0.9% $VO_{2\ peak}$) in a laboratory setting. Sixty minutes post-exercise, participants were given a meal followed by either a full, 75%, or 50% dose of rapid-acting insulin.

4 Three hours after meal ingestion, the highest levels of blood glucose were found with the 50% dose, (50% [10.4 ± 1.2] versus full [6.2 ± 0.7] and 75% [7.6 ± 1.2 mmol/L^{-1}]; P=0.029), which protected participants against hypoglycaemia (blood glucose ≤3.9; full, n=5; 75%, n=2; 50%, n=0).

5 Under free-living conditions, no episodes of hypoglycaemia were reported for a further 4 hours with the 50% dose, but the incidence of late and evening hypoglycaemia was similar with all doses.

6 The authors concluded that a 25% pre-exercise and 50% post-exercise rapid-acting insulin dose could protect people with T1D against early, but not late onset hypoglycaemia.

Campbell MD, Walker M, Trenell MI (2013) Large pre and postexercise rapid-acting insulin reductions preserves glycemia and prevents early- but not late-onset hypoglycemia in patients with type 1 diabetes. *Diabetes Care* 20 Mar [Epub ahead of print]

DIABETOLOGIA

The prevalence of monogenic diabetes in children with T1D

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

1 Monogenic diabetes (MD) refers to a group of rare diabetes types caused by single gene mutations. MD may be mistaken for T1D or T2D in clinical practice, and the current prevalence of MD in children with diabetes is unknown.

2 The authors set out to determine the prevalence of multiple common forms of MD in a cohort of children from the Norwegian Childhood Diabetes Registry.

3 A total of 2756 newly diagnosed children aged 0–14 years were included in the study and screened for gene mutations. The Norwegian maturity onset diabetes of the young (MODY) Registry was also searched for children diagnosed with MD that was already genetically verified.

4 Fifteen children were found to have a mutation in *HNF1A*. A mutation in *GCK* was detected in nine children and four had a mutation in *KCNJ11*. Only one child was harbouring a mutation in *INS*. No children were found to have a mutation in *MT-TL1*.

5 The minimum prevalence of MD in the cohort was 1.1%. An additional 15 children with a mutation in glucokinase-MODY were identified in the Norwegian MODY Registry, which increased the estimated minimum prevalence of MD in Norwegian children to 3.1/100 000.

6 The authors concluded that this study provides an accurate estimation of MD prevalence in the Norwegian child population, although the true prevalence of MD will remain unclear until all genes related to MD are screened for in population studies.

Irgens HU, Molnes J, Johansson BB et al (2013) Prevalence of monogenic diabetes in the population-based Norwegian childhood diabetes registry. *Diabetologia* **56**: 1512–9

DIABETES CARE

Comparing cystic fibrosis-related diabetes to T1D

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

1 As a result of improved treatment and life expectancy, cystic fibrosis-related diabetes (CFRD) has become the most common comorbidity associated with CF.

2 The authors conducted a multicentre analysis to compare the clinical characteristics and treatment choices between children (aged under 21 years) with CFRD and T1D.

3 Paediatric data (n=47 227) from the German/Austrian Diabetes Prospective Documentation Initiative registry were examined using multivariable mixed regression modelling.

4 Later onset diabetes was observed in children with CFRD (14.5 [interquartile range 11.8–16.3] years) compared to those with T1D (8.5 [interquartile range 4.9–11.8] years), with CFRD being more frequent in females (59.1% versus 47.5%; P<0.01).

5 Children with CFRD were found to have lower BMI standard deviation scores (20.85 [21.59–20.12] versus +0.52 [20.10 to +1.16]; P<0.01) and HbA_{1c} levels (52 mmol/mol [6.8%] versus 64 mmol/mol [7.9%]; P<0.01).

6 Short and long-acting insulin analogs were more frequently used in children with T1D (47% versus 39% and 37% versus 28% respectively; both P<0.05) who also self-monitored their blood glucose more often compared to children with CFRD (4.5 versus 3.5 times per day; P<0.01).

7 The authors concluded that infants with CFRD show distinctly different treatment choices and clinical characteristics compared to children with T1D.

Konrad K, Thon A, Fritsch M et al (2013) Comparison of cystic fibrosis-related diabetes with type 1 diabetes based on a German/Austrian Pediatric Diabetes Registry. *Diabetes Care* **36**: 879–86