Management & prevention of type 2 diabetes

Dysglycaemia and cardiovascular risk: Why testing for impaired glucose tolerance is unnecessary

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There is an old paradigm that suggests impaired fasting glucose (or impaired glucose tolerance [IGT]) is strongly associated with cardiovascular risk. The results of the DECODE study (Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe) are often quoted to support this notion, as in the recent European Society of Cardiology and European Association for the Study of Diabetes (ESC/EASD) guidelines (Rydén et al, 2013; summarised on page 48). DECODE reported a significant relationship between 2-hour plasma glucose in the IGT range and cardiovascular disease (CVD) mortality even after adjustment for other risk factors (Ning et al, 2010).

By contrast, DECODE could not show an independent association between fasting glucose and CVD risk once 2-hour glucose was taken into account. At face value, these results would suggest that knowing that an individual has IGT is important and, on the basis of such evidence, some have (sometimes strongly) argued that *all* individuals with CVD or at elevated risk should have an oral glucose tolerance test, not only to screen for diabetes but also to identify those with IGT (Rydén et al, 2013). Of course, one must be careful to appraise all relevant evidence from other cohorts to get a balanced view. Equally, before guidelines are formulated, one must ask whether IGT presence *meaningfully* reclassifies CVD risk over and above the traditional risk factors.

In this respect, the recent paper by Van Der Heijden et al (summarised alongside) is of interest. The authors examined predictors of recurrent cardiovascular events in people with diabetes and intermediate hyperglycaemia, the latter including individuals with IGT. Whilst the study was small in terms of event numbers, CVD event risk was significantly higher in people with diabetes but, interestingly, not so in those with intermediate hyperglycaemia in comparison to those with normal glucose metabolism. In a separate study, intermediate hyperglycaemia was also not predictive of CVD events in those with existing coronary heart disease (CAD), whereas, once again, existing diabetes was predictive (Lenzen et al, 2006).

Even if we accept that DECODE was larger in size and power than the two latter studies, clearly not all relevant studies concur and considerable uncertainty exists. Futhermore, DECODE did not examine if IGT presence meaningfully improved CVD risk reclassification, an important metric to guide the value of any test for clinical practice.

For these reasons, the new ESC/EASD guidelines correctly put HbA_{1c} (and fasting glucose) to the fore in their new guidelines. This is an important result since HbA_{1c} can be measured anytime and, thus, people with acute coronary syndromes can have their "chronic" glycaemic status checked anytime during their acute admission. By contrast, fasting glucose cannot be measured in the first 4 days given the inflammatory insult of the event. Of course, individuals with stable CVD or at elevated risk can have HbA_{1c} measured anytime, though a simple diabetes risk score (rapidly conducted) should be calculated first to determine if glycaemia testing is warranted, as per recent NICE guidance for the detection of diabetes and high risk of diabetes (Chatterton et al, 2012).

Finally, if one looks at all the relevant data, a new potential paradigm emerges; namely, that hyperglycaemia may only meaningfully accelerate CVD once individuals develop frank diabetes. This new understanding allows us to concentrate our efforts to prevent CVD in those without diabetes through the usual interventions (i.e. cholesterol, blood pressure, smoking) and to help prevent diabetes in those at elevated diabetes risk (HbA_{1c} 42–47 mmol/mol [6–6.4%]; fasting blood glucose 5.5–6.9 mmol/L). ■

Chatterton H et al (2012) *BMJ* **345**: e4624
Lenzen M et al (2006) *Eur Heart J* **27**: 2969–74
Ning F et al (2010) *Diabetes Care* **33**: 2211–6
Rydén L et al (2013) *Eur Heart J* **34**: 3035–87

Diabetes Care

Cardiovascular risk: Recurrent events

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

1 A sub-cohort of the Hoorn Study, which is based in the Netherlands, who experienced a first cardiovascular event after study entry (n=336) continued to be monitored, in respect to a recurrent cardiovascular event.

2 Those with normal glucose metabolism, intermediate hyperglycaemia and T2D were separated into three groups, and their absolute risk of a recurrent cardiovascular event was calculated.

3 In a median follow-up of 4.1 years, 44% of the cohort experienced a recurrent cardiovascular event.

4 The rate of recurrent events per 100 person-years for individuals with normal glucose metabolism was 7.2 (95% confidence intervals [CI]; 5.8–8.7); it was 9.8 (95% CI; 6.6–14.4) for individuals with intermediate hyperglycaemia and 12.5 (95% CI; 8.5–17.6) in individuals with T2D.

5 Baseline characteristics that were found to be positively associated with a higher risk of recurrent cardiovascular events included the following: age at first event; male sex; waist circumference, systolic blood pressure; HbA_{1c}; and family history of myocardial infarction.

6 Individuals with T2D are at a higher risk of a recurrent cardiovascular event compared to those with normal glucose control. People with intermediate hyperglycaemia are not at a higher risk of a cardiovascular event compared to those with normal glucose metabolism.

Van der Heijden AA, Van't Riet E, Bot SD et al (2013) Risk of a recurrent cardiovascular event in individuals with type 2 diabetes or intermediate hyperglycemia: the Hoorn Study. *Diabetes Care* **36**: 3498–502

Type 2 diabetes

"T2D diagnosis at <65 years was associated with worse glycaemic control than diagnosis at 65 years and older. However, the younger group also report fewer comorbidities."

Diabetes Care

Short leg length and T2D association

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

1 Data from the 3-year follow-up examination of the PROMISE (PROspective Metabolism and ISlet cell Evaluation) cohort study in Canada were used to determine if there was an association between short leg length (a marker of childhood deprivation) and metabolic disorder in adulthood.

2 All participants were at high risk of developing T2D and had a mean age of 54 years (n=462). Weight, weight at 18 years of age and waist circumference were significantly correlated with leg length.

3 Short leg length was independently associated with lower insulin sensitivity and beta-cell function.

4 This emphasises the potential of improving early life conditions to reduce the risk of T2D in later life.

Johnston LW, Harris SB, Retnakaran R et al (2013) Short leg length, a marker of early childhood deprivation, is associated with metabolic disorders underlying type 2 diabetes. *Diabetes Care* **36**: 3599–606

Diabetologia

Earlier T2D onset predicts worse glycaemic control

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

1 Adults participating in a nationwide US survey who self-reported T2D were split into two groups depending on their age at diabetes onset: <65 years versus ≥65 years. The authors studied whether younger age at diagnosis was associated with worse subsequent glycaemic control.

2 In total, data from 1438 people were analysed; 14.4% of those diagnosed before 65 years and 2.5% of those diagnosed after 65 years had an HbA_{1c} of >75 mmol/mol ([>9%] P<0.001).

3 After adjustment for baseline characteristics, the odds ratio (OR) an HbA_{1c} of >75 mmol/mol (>9%) for the younger group compared to the older group was 3.22 (95% confidence intervals [CI], 1.54–6.72).

4 Younger T2D diagnosis was associated with worse glycaemic control, but the younger group reported fewer comorbidities, so aggressive treatments could benefit this group.

Berkowitz SA, Meigs JB, Wexler DJ (2013) Age at type 2 diabetes onset and glycaemic control. *Diabetologia* **56**: 2593–600

Diabetic Medicine

Detecting insulin deficiency in T2D

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

1 Urinary C-peptide creatinine ratios were used to detect absolute insulin deficiency in people with T2D.

2 In total, 191 people in the UK with insulin-treated T2D provided urine samples 2 hours after the largest meal of the day and their urinary C-peptide creatinine ratio was calculated. If the ratio was ≤0.2 nmol/mol (suggesting absolute insulin deficiency), the test was repeated.

3 The test was repeated in nine people, and a standardised mixed-meal tolerance test with 90-minute stimulated serum C-peptide measurements was performed to confirm insulin deficiency.

4 Five people (2.7%) were confirmed as having absolute insulin deficiency if the stimulated serum C-peptide measurement was <0.2 nmol/L.

5 Those that had absolute insulin deficiency had a significantly shorter time from diagnosis to insulin treatment, and a lower BMI. This is a practical, non-invasive indicator test for endogenous insulin production.

Hope SV, Jones AG, Goodchild E et al (2013) Urinary C-peptide creatinine ratio detects absolute insulin deficiency in type 2 diabetes. *Diabet Med* **30**: 1342–48

Diabetes Care

Naltrexone/bupropion therapy for weight loss in T2D?

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

1 In a phase III trial, the efficacy and safety of 32 mg naltrexone sustained release/360 mg bupropion sustained release (NB) was investigated as a weight loss treatment in overweight or obese people with T2D.

2 NB therapy is believed to influence the mesolimbic dopaminergic reward system, which can modulate reward behaviours such as food intake.

3 The trial lasted 56 weeks and was double-blinded and placebo-controlled. In total, 505 people were randomised in a 2:1 ratio to NB and placebo therapy respectively.

4 The NB group achieved a significantly greater weight reduction than the placebo group, –5.0% versus –1.8% respectively. More participants in the NB group also achieved ≥5.0% weight loss than the placebo group at week 56 (P<0.001 for both).

5 The NB cohort also had far greater improved HbA_{1c}, and a greater percentage of the cohort achieved an HbA_{1c} of 53 mmol/mol (<7%) compared to the placebo cohort (P<0.001 for both).

6 Over the study period, 47.8% of participants in the NB group discontinued the treatment. The most common adverse events were nausea, constipation, vomiting and diarrhoea. Nausea was the most reported, and accounted for 9.6% of those that withdrew. The majority of these cases withdrew in the first 4 weeks of treatment.

Hollander P, Gupta AK, Plodkowski R et al (2013) Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care* **36**: 4022–9