Impaired glucose metabolism: A tale of two conditions

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This expert review article by Abdul-Ghani and colleagues (see right) gives a summary of the different characteristics of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), both from epidemiological studies and metabolic characterisation studies.

Epidemiological studies demonstrate that although both IGT and IFG are intermediate states between normal glucose tolerance and overt type 2 diabetes, they define two distinct populations with only partial overlap. Over half of IFG subjects have a 2-hour glucose below 7.8 mmol/l and only 20–25 % of people with IGT have a fasting plasma glucose above 6.1 mmol/l. The prevalence of both conditions varies in different ethnic groups, but IFG always has a lower prevalence than IGT in all populations. The conditions also differ in their age and sex distributions. This suggests that they may have different pathophysiological aetiologies.

After reviewing published studies on the metabolic characterisation of both IGT and IFG the authors state that although the conditions are both insulin resistance states, they differ in the site of insulin resistance. Those with IFG predominantly have hepatic insulin resistance and normal muscle insulin sensitivity, while individuals with IGT have normal-to-slightly-reduced hepatic insulin sensitivity and moderate-to-severe muscle insulin resistance.

The pattern of impaired insulin secretion also differs between the two conditions. Those with isolated IFG have a decrease in the early-phase insulin response; however, late-phase insulin response during an oral glucose-tolerance test is less severely impaired than in IGT. Those with IGT have severe defects in both early- and late-phase insulin response.

This is all fascinating information but has it any practical value at present? Well, the authors conclude that it could suggest a different pharmacological approach to preventing conversion from impaired glucose metabolism to overt type 2 diabetes. Those with IFG might respond best to metformin, whereas those with IGT might respond better to glitazones, perhaps in combination with a glucagon-like peptide 1 analogue!

DIABETES CARE

Structured personal care only affects women's HbA_{1c}

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

1 Previous studies have shown that men and women with diabetes differ in their attitudes and behaviour towards the condition.

2 This paper outlines a sub-group analysis of the Diabetes Care in General Practice cluster-randomised controlled trial.

3 Nearly 900 primary care diabetes patients were randomised to receive either structured personal care or routine care from their GPs. Structured personal care involved consultations every 3 months and personalised goal-setting.

4 For the female participants there was a statistically significant difference in HbA_{1c} between the treatment groups (median values were 8.4 % versus 9.2 % for the structured personal care and routine care groups, respectively; $P<0.0001$). For men, the corresponding values were 8.5 % and 8.9 % ($P=0.052$).

5 The authors concluded that this effect might only be observed in women possibly because they are more likely to attend regular follow-up sessions, and have a more adaptive attitude to diabetes, than men.

Nielsen AB, De Fine Olivarius N, Gannik D et al (2006) Structured personal diabetes care in primary health care affects only women's HbA1c. *Diabetes Care* **29**(5): 963–9

DIABETES CARE

Pathogenesis of IGT and IFG

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

1 The pathway from normal glucose tolerance to type 2 diabetes also includes the intermediate states of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).

2 Previous epidemiological studies have shown that IFG and IGT are found in distinct populations with only partial overlap. This suggests that IFG and IGT result from differing metabolic abnormalities.

3 The authors reviewed clinical studies which showed that the site of insulin resistance varies between the conditions. In IGT, muscle insulin resistance with mild hepatic insulin resistance is observed, while in IFG marked hepatic insulin resistance is seen, with little, if any, impairment in muscle insulin resistance.

4 Furthermore, while an impaired early-phase insulin response has been observed in both IGT and IFG, a reduced late-phase response has been seen in IGT alone.

5 These differences in the metabolic characteristics of IGT, IFG and combined glucose intolerance (the combination of IFG and IGT) help to explain the differing plasma glucose profiles observed following glucose ingestion in these conditions.

6 These insights offer guidance on how best to slow or prevent the progression from impaired glucose metabolism to overt type 2 diabetes. For example, those with IFG are likely to benefit most from agents addressing hepatic insulin resistance. In contrast, those with IGT are perhaps more likely to respond to agents addressing skeletal muscle insulin resistance.

Abdul-Ghani MA, Tripathy DD, DeFronzo RA (2006) Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* **29**(5): 1130–9

DIABETES CARE

Extended-release metformin is as safe and efficacious as immediate-release formulation

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

1 Metformin has been used as a glucose-lowering medication for many years. It is a first-line therapy in type 2 diabetes.

2 This study aimed to assess the safety and efficacy of a novel extended-release formulation of the drug in type 2 diabetes. This new formulation could potentially enable once-daily administration of metformin, compared with the two- or three-times daily administration of the immediate-release formulation.

3 This 24-week, randomised, double-blind, active-controlled trial randomly assigned people with type 2 diabetes to receive either extended-release (1500 mg/day once daily, 1500 mg/day twice daily or 2000 mg/day once daily) or immediate-release metformin (1500 mg/day twice daily). Participants were either drug-naive or had previously been treated with oral monotherapy (not metformin).

4 Mean HbA_{1c} levels had decreased significantly in all treatment groups by week 12 ($P<0.001$). The reduction in HbA_{1c} observed from baseline to endpoint in the group receiving 2000 mg/day extended-release metformin was significantly different from that seen in the immediate-release group (difference in reduction –0.36 % [98.4 % confidence interval –0.65 to –0.06]).

5 Overall, the rate of gastrointestinal adverse events in week 1 was similar between the treatment groups. However, there was a significant difference in the incidence of nausea, with those taking extended-release metformin experiencing less than those receiving immediate-release metformin ($P<0.05$).

6 The investigators concluded that the extended-release formulation of metformin, taken once or twice daily for 24 weeks, is as safe and efficacious as immediate-release metformin.

Schwartz S, Fonseca V, Berner B et al (2006) Efficacy, tolerability, and safety of a novel once-daily extended-release metformin in patients with type 2 diabetes. *Diabetes Care* **29**: 759–64

DIABETES CARE

Health professionals recognise the importance of exercise

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

1 It is well known that regular physical activity is important for the management and prevention of type 2 diabetes. The rationale for this study was to assess the extent to which individuals with, or at high risk of, diabetes are advised to exercise more by professionals.

2 The Medical Expenditure Panel Survey of 2002, which is nationally representative of the US population, was used as the data source. Over 26 800 adults responded when asked if a doctor had ever advised them to exercise more.

3 Self-reported information from the survey was used to identify people with diabetes and those with risk factors for type 2 diabetes (e.g. age ≥45 years, BMI ≥25 kg/m^2, diagnosis of hypertension, cardiovascular disease).

4 The investigators found that 73 % of adults with diabetes reported that they had been advised to exercise more by a health professional. The corresponding proportion for those without diabetes was 31 % overall. However, the rate of advice in this population did increase with the number of diabetes risk factors.

5 Increasing age and income, and higher education levels, were linked with an increased likelihood of receiving exercise advice in those without diabetes.

6 In contrast, in those with diabetes, the likelihood of receiving advice did not differ significantly according to age, education or income. People from a Hispanic background were, however, less likely to be offered advice than non-Hispanics.

7 The authors concluded that health professionals seem to recognise the importance of exercise in diabetes and in those at high risk of the condition.

Morrato EH, Hill JO, Wyatt HR et al (2006) Are health care professionals advising patients with diabetes or at risk for developing diabetes to exercise more? *Diabetes Care* **29**: 543–8

DIABETIC MEDICINE

Mortality in type 2 diabetes in the UK

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

1 Previous estimates of mortality in type 2 diabetes have been affected by under-reporting of diabetes on death certificates. There is conflicting evidence on the impact of obesity on mortality in type 2 diabetes.

2 This study therefore aimed to estimate mortality in type 2 diabetes (and the impact of obesity on this) using a large cohort of participants selected from the General Practice Research Database.

3 Baseline in the study was 1 January 1992. People aged 35–89 years with type 2 diabetes (n=44 230) at baseline were selected, along with a comparison group without diabetes (n=219 797). Deaths occurring in the period until October 1999 were identified.

4 All-cause mortality was higher in those with type 2 diabetes compared with those without (hazard ratio, [HR] 1.93; 95% confidence interval [CI], 1.89–1.97). In men this HR was 1.77 (95% CI, 1.72–1.83), while in women it was 2.13 (95% CI, 2.06–2.20).

5 In a multivariate analysis of people with type 2 diabetes for whom there were adequate data (n=28 725), it was found that smoking was associated with an HR of 1.50 (95% CI, 1.41–1.61). Using people with BMI 20–24 kg/m^2 as a reference, a BMI of 35–54 kg/m^2 was associated with an HR of 1.43 (95% CI, 1.28–1.59).

6 The authors concluded that, relative to people without diabetes, those with type 2 diabetes have almost double the rate of mortality. Obesity and smoking heighten this mortality risk.

Mulnier HE, Seaman HE, Raleigh VS et al (2006) Mortality in people with type 2 diabetes in the UK. *Diabetic Medicine* **23**: 516–21

DIABETIC MEDICINE

Beliefs about hypoglycaemic agents in type 2

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

1 The authors of this study aimed to investigate the correlation of people with type 2 diabetes' beliefs about medication with self-reported medication adherence.

2 These issues were explored with a questionnaire among people with type 2 diabetes aged ≥40 years. The questionnaire had 121 responses.

3 The majority of respondents strongly agreed with positive statements about the benefits of medication.

4 Two beliefs, concerning changes to daily routine and weight gain, were significantly associated with reduced adherence to medication (P<0.001 and P<0.05, respectively).

Farmer A, Kinmouth A-L, Sutton S (2006) Measuring beliefs about taking hypoglycaemic medication among people with type 2 diabetes. *Diabetic Medicine* **23**: 265–75

ANNALS OF PHARMACOTHERAPY

Depression impairs adherence to OHAs

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

1 This study aimed to examine the effect of depression on adherence to oral hypoglycaemic agents (OHAs) in people with newly diagnosed type 2 diabetes.

2 The investigators identified people newly diagnosed with diabetes (n=1326) during a 4-year period using a medical and prescription claims database. The presence or absence of pre-existing depression was also noted (n=471 versus 855, respectively).

3 Adherence to OHAs was measured over a period of 12 months from the first OHA prescription. Two adherence indices were constructed.

4 The study found that people with depression had significantly lower adherence with OHA medication than those without (86% [index 1] and 66% [index 2] adherence versus 89% and 73%, respectively).

5 The authors concluded that depression significantly impairs adherence with OHAs in newly diagnosed type 2 diabetes.

Kalsekar ID, Madhavan SS, Amonkar MM et al (2006) Depression in patients with type 2 diabetes: impact on adherence to oral hypoglycaemic agents. *Annals of Pharmacotherapy* **40**: 605–11

ARCHIVES OF MEDICAL RESEARCH

Insulin glargine versus NPH, both with glimepiride

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

1 In this study, the investigators compared the safety and efficacy of insulin glargine plus glimepiride with that of NPH insulin plus glimepiride in people with type 2 diabetes poorly controlled on oral antidiabetic drugs (OADs).

2 Using a titration algorithm, people with type 2 diabetes and HbA_{1c} ≥7.5 and ≤10.5% were randomised to receive one of the two treatment combinations for 24 weeks (glargine group: n=231, NPH group: n=250).

3 HbA_{1c} was lowered by a similar amount in each treatment arm. However, fewer people in the glargine arm experienced nocturnal hypoglycaemia than in the NPH group (16.9% versus 30.0%, respectively; P<0.01).

Eliaschewitz FG, Calvo C, Valbuena H et al (2006) Therapy in type 2 diabetes: insulin glargine vs. NPH insulin both in combination with glimepiride. *Archives of Medical Research* **37**: 495–501

'The authors concluded that depression significantly impairs adherence with oral hypoglycaemic agents in newly diagnosed type 2 diabetes.'

'Relative to people without diabetes, those with type 2 diabetes have almost double the rate of mortality.'