Diabetes journals

Impaired glucose tolerance: 'does the ticking clock go backward as well as forward?'

Mark Kearney, Cardiologist, King's College Hospital, London

In 1990, Steven Haffner proposed his 'ticking clock' hypothesis; that the insulin resistance syndrome predates the onset of overt diabetes and predisposes to the development of atherosclerosis over a period of time before diabetes/loss of glucose regulation becomes manifest.

The insulin resistance syndrome, a collection of pro-atherogenic abnormalities of blood pressure regulation, lipids and impaired glucose homeostasis, is hence an attractive target to prevent the development of both atherosclerosis and diabetes.

A fundamental question is whether or not patients can have an improvement in insulin sensitivity and at the same time benefit from an improvement in their atherogenic risk factor profile, rather than move down the spiral of worsening insulin sensitivity into diabetes. Identifying such patients may enable us to focus on what makes them improve.

The report by Wong et al addressed this issue in an elegant longitudinal study of patients with impaired and normal glucose tolerance followed up for 8 years.

This study confirmed a number of important points and demonstrated some novel findings:

- Over 30% of patients with impaired glucose tolerance (defined as 2 h, post-glucose-load glucose >7.8 mmol/l and <11.1 mmol/l) will develop diabetes during 8 years of follow up
- More than one-third of patients with impaired glucose tolerance will revert back to normal glucose tolerance
- Patients reverting back to normal glucose tolerance had an improvement in triglycerides, high-density lipoprotein and plasma insulin
- Despite this improvement, these patients remained more obese and hypertensive than patients with normal glucose tolerance who remained glucocompetent.

This simple study reinforces the potentially progressive nature of impaired glucose tolerance. Obesity/insulin resistance is a complex disorder with a number of different targets to reduce the risk of developing atherosclerosis. Wong et al demonstrate that the ticking clock can go both ways. However, even if the clock goes backwards and glucose tolerance improves, one should be vigilant about the presence of risk factors — and as usual it seems that obesity is central to the problem.

JOURNAL OF DIABETES AND ITS COMPLICATIONS

Decreased muscle perfusion causes foot problems

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

1 This study investigated the prevalence of poor muscle perfusion of the lower extremities in patients with type 2 diabetes with abnormal myocardial perfusion and more cardiovascular risk factors.

2 A non-invasive radionuclide was used to evaluate the anterior tibial muscle perfusion of 60 patients with type 2 diabetes without peripheral vascular disease.

3 Patients were grouped according to myocardial perfusion and cardiovascular risk. The normal control group comprised 30 patients.

4 There was a significant difference between the muscle perfusions in patients with type 2 diabetes and the normal controls, the patients with abnormal myocardial perfusion and those with normal myocardial perfusion, and the patients with more cardiovascular risk factors and those with less risk factors.

5 Muscle perfusion in the lower extremities of patients with type 2 diabetes without symptoms of peripheral vascular disease is significantly decreased, relating to abnormal myocardial perfusion.

Lin CC, Ding HJ, Yen RF et al (2003) High prevalence of asymptomatically poor muscle perfusion of lower extremities measured in type 2 diabetes patients with abnormal myocardial perfusion. *Journal of Diabetes and its Complications* **17**: 365–68

DIABETES CARE

Impaired glucose tolerance associated with CVD risk factors

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

1 The aim of this study was to determine what happens to cardiovascular disease (CVD) risk factors in patients when their glucose tolerance returns from impaired glucose tolerance (IGT) to normal glucose tolerance (NGT). Do the factors reverse or do they remain the same, such that these individuals continue to be at increased risk of CVD?

2 Patients with IGT and NGT were identified from a cross-sectional survey conducted in 1992. Patients with IGT (297) and NGT (298; 65%) were re-examined in 2000. Glucose tolerance, anthropometric data, serum lipids, blood pressure and insulin resistance were determined at baseline and at the follow-up examination.

3 Of patients with NGT, 14% progressed to IGT and 4.3% to diabetes over 8 years. Of those with IGT, 41.4% reverted to NGT, 23% remained IGT and 35.1% developed diabetes.

4 Obesity, hypertriglyceridaemia, higher blood pressure, increased insulin resistance and lower levels of high-density lipoprotein cholesterol at baseline were associated with worsening glucose tolerance in both IGT and NGT patients.

5 Patients with IGT who reverted to NGT remained more obese and had higher blood pressure than those with NGT in both 1992 and 2000.

6 Some CVD risk factors associated with IGT and with the risk of future diabetes normalise when glucose tolerance normalises.

Wong MS, Gu K, Heng D et al (2003) The Singapore impaired glucose tolerance follow-up study: does the ticking clock go backward as well as forward? *Diabetes Care* **26**: 3024–30

'The primary objective of the Veterans Affairs Diabetes Trial (VADT) is the assessment of the effect of intensive glycaemic treatment on cardiovascular (CV) events.'

'Adults with early-onset type 2 diabetes were 80% more likely to begin insulin therapy than those with usual-onset type 2 diabetes.'

JOURNAL OF DIABETES AND ITS COMPLICATIONS

Veterans Affairs Diabetes Trial looks at glycaemic control

Readability	✓✓✓
Applicability to practice	
WOW! factor	✓

1 The primary objective of the Veterans Affairs Diabetes Trial (VADT) is the assessment of the effect of intensive glycaemic treatment on cardiovascular (CV) events. Other objectives are effects on microangiopathy, quality of life and cost-effectiveness.

2 The VADT, started in December 2000, is enrolling 1700 men and women previously uncontrolled on insulin or maximum doses of oral agents. Accrual is 2 years, and follow up is 5–7 years, with visits every 1.5 months. The study has a power of 86% to detect a 21% relative reduction in major CV events.

3 Patients are randomised to an intensive group aiming at normal HbA_{1c} levels, or to a standard group with usual, improved glycaemic control. Both groups receive step therapy to achieve goals. Strict control of blood pressure and dyslipidaemia, daily aspirin, diet and education are identical in both groups.

4 Plasma fibrinogen, plasminogen-activating inhibitor, lipids, renal function parameters and ECGs are measured throughout.

5 Stereo retinal photographs are obtained at entry and 5 years, eye examinations yearly, and intervention as needed to prevent visual deterioration.

6 Recruitment is proceeding on schedule: the mean HbA_{1c} at entry is 9.4 and mean duration of diagnosed diabetes is 11 years.

Abraira C, Duckworth W, McCarren M et al (2003) Design of the cooperative study on glycaemic control and complications in diabetes mellitus type 2. Veterans Affairs Diabetes Trial. *Journal of Diabetes and its Complications* 17: 314–22

DIABETES CARE

Oestrogen therapy decreases CV risk

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

1 This study evaluated the association between oestrogen therapy and risk of cardiovascular (CV) events among women with type 2 diabetes.

2 A study was conducted among 6017 women aged 45–80 years with type 2 diabetes from 1 January 1986 to 31 December 1992. CV outcomes were ascertained through 31 December 1998. Use of oestrogen and progestin was derived from clinical records. Median follow up was 6.8 years.

3 Use of oestrogen was associated with a decreased risk of CV events compared with never having used oestrogen.

4 Results show an association of oestrogen therapy with decreased risk of CV events among women with type 2 diabetes.

Newton KM, LaCroix AZ, Heckbert SR et al (2003) Estrogen therapy and risk of cardiovascular events among women with type 2 diabetes. *Diabetes Care* 26: 2810–16

DIABETES CARE

Complications increase with early-onset diabetes

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

1 The aim was to determine whether adults diagnosed with type 2 diabetes from 18–44 years more aggressively developed clinical complications after diagnosis than adults diagnosed ≥45 years of age.

2 Outcomes were compared among 7844 adults newly diagnosed with type 2 diabetes between 1996–98 who were followed up for incident complications through December 2001.

3 Adults with early-onset type 2 diabetes were 80% more likely to begin insulin therapy than those with usual-onset type 2 diabetes. Development of a myocardial infarction in early-onset type 2 diabetes was 14-fold higher than in controls.

4 Young adults with early-onset type 2 diabetes have a much higher risk of cardiovascular disease.

Hillier TA, Pedula KL (2003) Complications in young adults with early-onset type 2 diabetes. Diabetes Care 26: 2999–3005

DIABETES

Metabolic syndrome detects insulin resistance

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

1 It is generally believed that individuals with the metabolic syndrome (MetS) have insulin resistance (IR). This study examined associations of MetS with measures of insulin sensitivity and secretion among 1035 patients without diabetes.

2 MetS definitions were significantly associated with risk of being in the lowest quartile of directly measured insulin sensitivity. MetS definitions were also significantly associated with risk of being in the lowest quartile of insulin sensitivity-adjusted acute insulin response (AIR) and disposition index (DI).

3 The MetS criteria identified individuals without diabetes with low insulin sensitivity, with the association being stronger using the WHO definition. The definitions are generally less useful for identifying those with low AIR or DI.

Hanley AJG, Wagenknecht LE, D'Agostino RB, Zinman B, Haffner SM (2003) Identification of subjects with insulin resistance and β-cell dysfunction using alternative definitions of the metabolic syndrome. *Diabetes* 52: 2740–7

'Basal platelet nitric oxide synthase activity was lower in patients with diabetes than in controls, although no corresponding difference was seen in basal platelet cyclic GMP.'

'Nitric oxide generation stimulated by β-adrenoceptors and adenylyl cyclase is impaired in platelets of people with type 2 diabetes.'

JOURNAL OF DIABETES AND ITS COMPLICATIONS

CVD in patients with diabetes increases hospital costs

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

1 The objective was to measure the impact of diabetes on hospital resource use and expenditures in patients hospitalised for cardiovascular disease (CVD).

2 This was a study of 4865 hospitalisations for CVD over 2 years. Data on the presence of diabetes, length of stay, readmissions, mortality and costs were obtained through retrospective chart review.

3 On average, patients with diabetes hospitalised for CVD have longer hospital stays and greater risk of short-term readmission, and are more costly than patients without diabetes.

4 However, in-hospital mortality risk in patients hospitalised by CVD is no greater in patients with diabetes than in patients without diabetes.

Carral F, Aguilar M, Olveira G et al (2003) Increased hospital expenditures in diabetic patients hospitalised for cardiovascular diseases. *Journal of Diabetes and its Complications* **17**: 331–36

DIABETES CARE

Pravastatin therapy prevents CV events in diabetes

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

1 The study looked at the effects of pravastatin therapy over 6 years on the risk of cardiovascular (CV) outcomes in 1077 patients with diabetes and 940 patients with impaired fasting glucose.

2 Pravastatin therapy reduced the risk of any CV event from 52.7% to 45.2% in patients with diabetes, and from 45.7% to 37.1% in the impaired fasting glucose group. Pravastatin reduced the risk of stroke from 9.9% to 6.3% in the group with diabetes, and from 5.4% to 3.4% in the impaired fasting glucose group.

3 Cholesterol-lowering treatment with pravastatin therapy prevents CV events, including stroke, in patients with diabetes or impaired fasting glucose and established coronary heart disease.

Keech A, Colquhoun D, Best J et al (2003) Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose. *Diabetes Care* **26**: 2713–21

DIABETES CARE

Leptin and TNF-α affect insulin resistance

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

1 Leptin and tumour necrosis factor (TNF)-α are associated with insulin resistance and cardiovascular disease, mediated via overproduction of the chemokine involved in the pathogenesis of atherosclerosis (monocyte chemoattracting protein [MCP]-1/CCL2]).

2 Fasting plasma leptin, soluble TNF-α receptor-2 and MCP-1/CCL2 were measured in 207 middle-aged women (53 with type 2 diabetes, 42 with impaired glucose tolerance and 112 with normal glucose tolerance) to assess their relationship with markers of atherosclerosis and, over 7 years, associations with cardiovascular disease.

3 MCP-1/CCL2, leptin and TNF-α receptor-2 were all related to biochemical risk markers of atherosclerosis. MCP-1/CCL2 concentration was the only one to be increased in type 2 diabetes. Leptin was associated with a protective effect.

Piemonti L, Calori G, Mercalli A et al (2003) Fasting plasma leptin, tumour necrosis factor-α receptor-2 and monocyte chemo-attracting protein 1 concentration in a population of glucose-tolerant and glucose-intolerant women. *Diabetes Care* **26**: 2883–9

DIABETOLOGIA

Diabetes impairs nitric oxide generation

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

1 Patients with type 2 diabetes have been shown to have reduced basal platelet nitric oxide synthase activity, which is a possible contributor to the vascular complications seen in the disease.

2 The authors investigated platelet nitric oxide generation stimulated by β-adrenoceptors and adenylyl cyclase in patients with type 2 diabetes and in control subjects.

3 Platelets isolated from the blood of nine patients with type 2 diabetes and nine healthy controls were treated with isoproterenol, forskolin or vehicle. Platelet nitric oxide synthase activity was measured by L-arginine–L-citrulline conversion, cyclic GMP content by radioimmunoassay and nitric oxide synthase type 3 expression by western blotting.

4 Basal platelet nitric oxide synthase activity was lower in patients with diabetes than in controls, although no corresponding difference was seen in basal platelet cyclic GMP.

5 In controls, isoproterenol and forskolin increased platelet nitric oxide synthase activity and cyclic GMP. This effect was not achieved in patients with diabetes. Platelet nitric oxide synthase type 3 expression was not different in patients with diabetes and controls.

6 Nitric oxide generation stimulated by β-adrenoceptors and adenylyl cyclase is impaired in platelets of people with type 2 diabetes, possibly contributing to thrombotic and atherosclerotic complications.

Queen LR, Ji Y, Goubareva I, Ferro A (2003) Nitric oxide generation mediated by β-adrenoceptors is impaired in platelets from patients with type 2 diabetes mellitus. *Diabetologia* **46**: 1474–82