Management of type 1 diabetes

Insulin effects in nondiabetic relatives of patients with type 1 diabetes

Adrian Scott, Consultant Physician, Derbyshire Royal Infirmary

The Diabetes Prevention Trial and the recently reported ENDIT Trial (EASD, Budapest, September 2002) are landmark studies in the field of prevention of type 1 diabetes. Although both studies are 'negative' in that the intervention failed to protect against the development of diabetes in persons at high risk for type 1 diabetes, they illustrate the importance of undertaking large randomised studies even if (and especially if) smaller, and therefore underpowered, studies seem convincingly positive.

Previous investigations in animals, and small pilot studies of insulin therapy for the prevention of diabetes in humans, had convinced some clinicians to initiate insulin therapy in the relatives of people with diabetes, particularly in siblings who were positive for islet-cell antibodies (ICAs).

The hypothesis was that insulin (administered parenterally or orally) might act metabolically (by resting the beta cells or immunologically. The study numbers were awe-inspiring: more than 84000 first- and second-degree relatives of patients with type 1 diabetes were screened for islet cell antibodies. Over 3000 were ICA positive. Of these, 339 underwent randomisation and 169 were eventually assigned to the intervention.

It is easy to dismiss such studies with a glance at the conclusions, but to do so is to miss the great contribution these studies make to our understanding of the pathogenesis of type 1 diabetes and the risks for the relatives of these patients. The possibility remains that the course of diabetes might have been modified even though prevention was not achieved, and the enthusiasm of the Study Group is undaunted: it believes that the ongoing Diabetes Prevention Trial -1 oral insulin trial might be more successful.

How much more intellectually rigorous was the design of this trial compared with so many others these days in which the main purpose is not to answer a well-formed hypothesis but to market the latest 'me-too' molecule before it comes off patent. Congratulations to Jay Skyler and the Diabetes Prevention Trial – Type 1 Diabetes Study Group.

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

Insulin therapy in nondiabetic relatives

1 To assess whether insulin therapy can delay or prevent diabetes in the nondiabetic relatives of patients with diabetes, 84228 first- and second-degree relatives were screened for islet-cell antibodies.

2 Of this initial sample, 3152 tested positive. Of these, 2103 underwent genetic, immunological and metabolic staging to quantify their risk.

3 There was a projected 5-year risk of >50% in 372 of the subjects. Of these, 339 were randomly assigned to undergo either close observation or an intervention comprising insulin therapy.

4 Oral glucose tolerance tests were performed every 6 months, and the median follow-up period was 3.7 years.

5 Diabetes was diagnosed in 69 subjects in the intervention group and in 70 subjects in the observation group.

6 The annualised rate of progression to diabetes was 15.1% in the intervention group and 14.6% in the observation group.

7 Progression to diabetes occurred at a faster rate in subjects with abnormal baseline glucose tolerance than in those with normal glucose tolerance.

8 Diabetes is predicted to continue to develop in high-risk subjects at the rates observed in this study. Subjects with a projected 5-year risk of >50% therefore have a 10-year risk of 90%.

9 In conclusion, for people at high risk of diabetes, therapy with insulin at the dosage used in this study does not delay or prevent type 1 diabetes.

10 However, participation in the trial probably increases the relatives' awareness of their level of risk, which makes it more likely that they will test their blood glucose. Also, having an oral glucose tolerance test every 6 months increases the likelihood of early diagnosis of diabetes.

Diabetes Prevention Trial – Type 1 Diabetes Study Group (2002) Effects of insulin in relatives of patients with type 1 diabetes mellitus. *The New England Journal of Medicine* **346**(22): 1685–91

'Rates of foot examination and lipid measurement in a routine outpatient clinic were below those recommended.'

'QTc prolongation and a larger QTc dispersion are already present in a significant proportion of children and adolescents with diabetes.'

METABOLISM

Glycaemic control with biphasic insulin aspart

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

1 To investigate the ability of biphasic insulin aspart (BIAsp) to control postprandial hyperglycaemia and hyperlipidaemia, 50 patients with type 1 diabetes were studied on three separate days.

2 The meal-test comparison was used to compare BIAsp injected immediately before the meal, biphasic human insulin injected 30 minutes before the meal (BHI30), and BHI injected immediately before the meal (BHI).

3 BIAsp reduced the area under the baseline-adjusted 4-hour postprandial serum glucose curve by 23% and 9% more than BHI and BHI30, respectively.

4 The maximum serum glucose concentration was lower for BIA than for BHI given at the meal, and the time taken to reach maximal serum glucose concentrations was approximately 20 minutes shorter for BIAsp compared with BHI and BHI30.

5 The improved ability of BIAsp to control postprandial blood glucose levels reflects the fact that absorption of BIAsp at 0–4 hours after injection was significantly faster compared with BHI30.

6 There were no significant differences between the treatments with respect to postprandial levels of free fatty acids or triglycerides.

Hermansen K, Vaaler S, Madsbad S, Dalgaard M et al (2002) Postprandial glycemic control with biphasic insulin aspart in patients with type 1 diabetes. *Metabolism* **51** (7): 896–900

DIABETES RESEARCH AND CLINICAL PRACTICE

Improving the quality of diabetes treatment

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

1 It is known that good metabolic control, careful monitoring of late diabetic complications and early intervention against cardiovascular risk factors improve the prognosis in diabetic patients.

2 This study analysed the treatment quality in a routine outpatient clinic of 2011 type 1 diabetics.

3 HbA_{1c} levels were measured at least once a year in >99.5% of the patients. Mean HbA_{1c} was 8.6–8.8% over 3 years.

4 Urinary albumin excretion was measured in 80.5–87.1% of patients over the 3 years, and blood pressure in 71.4–79.8%.

5 Foot examinations and fundus photography were done at least once in 84.7 and 88.6% of the patients, respectively.

6 The study concluded that the frequency of measurement of some, but not all, important clinical variables was high.

7 More specifically, HbA_{1c}, blood glucose and body mass index were measured more frequently than recommended, and measurement rates of urinary albumin excretion and blood pressure were nearly as recommended. At present, however, rates of foot examination and lipid measurement are below those recommended.

Jensen T, Musaeus L, Molsing B, Lyholm B, Mandrup-Poulsen T (2002) Process measures and outcome research as tools for future improvement of diabetes treatment quality. *Diabetes Research and Clinical Practice* **56**: 207–11

THE JOURNAL OF PEDIATRICS

QTc interval prolongation and QTc dispersion

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

1 Diabetic autonomic nervous system failure is a common complication of diabetes.

2 QT intervals measure alterations in cardiac sympathetic innervation. A longer QT interval is associated with diabetic complications and increased mortality rate in adults.

3 QT dispersion assesses delayed ventricular depolarisation and repolarisation heterogeneity in adult diabetic patients

4 This study set out to evaluate whether QT interval, QT interval correlated for heart rate (QTc) and QTc dispersion changes are already present in children and adolescents with diabetes.

5 The study included 60 subjects with type 1 diabetes and 63 control subjects.

6 Diabetics had longer QTc intervals and larger QTc dispersions than controls.

7 QTc and QTc dispersion were not influenced by the level of metabolic control, age or diabetes duration.

8 It was concluded that QTc prolongation and a larger QTc dispersion are already present in a significant proportion of children and adolescents with diabetes.

Suys BE, Huybrechts SJA, De Wolf D, De Beeck LO et al (2002) QTc interval prolongation and QTc dispersion in children and adolescents with type 1 diabetes. *The Journal of Pediatrics* **141** (1): 59–61

CIRCULATION

Glycoprotein IIb/IIIa receptor inhibitors

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

a worse outcome after percutaneous coronary angioplasty and stenting.

2 Abciximab inhibits the platelet glycoprotein IIb/IIIq receptor, and improves early and late outcomes in diabetic patients undergoing percutaneous coronary intervention (PCI).

3 To assess whether the clinical benefit associated with abciximab also applies to small-molecular agents such as tirofiban, 1117 diabetic patients undergoing PCI with stent implantation were randomised to tirofiban or abciximab.

4 The incidence of death, myocardial infarction or urgent target vessel revascularisation (TVR) at 30 days in the two groups were comparable.

5 At 6 months, the composite of death, myocardial infarction or any TVR again occurred in similar percentages in the two groups.

6 One-year mortality in the two groups was comparable.

7 In conclusion, in diabetic patients undergoing PCI, tirofiban and abciximab were associated with comparable event rates, including similar rates of 6-month TVR and 1-year mortality.

8 This suggests that the non-glycoprotein IIb/IIIa properties of abciximab do not translate into a discernible long-term clinical benefit in diabetic patients, and that the long-term mortality benefit of platelet GP IIb/IIIa receptor inhibitor in diabetic patients might not be linked to abciximab-specific effects.

Roffi M, Moliterno DJ, Meier B, Powers ER et al (2002) Impact of different platelet glycoprotein IIb/IIIa receptor inhibitors among diabetic patients undergoing percutaneous coronary intervention: do Tirofiban and ReoPro give similar efficacy outcomes trial (TARGET) 1-year follow-up. *Circulation* **105**: 2730–6

'Results suggest that the long-term mortality benefit of platelet GP IIb/IIIa receptor inhibitor among diabetic patients might not be linked to abciximab-specific effects.'

ANNALS OF EPIDEMIOLOGY

Predicting mortality in type 1 diabetes

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

1 This study examined the abilities of estimated glucose disposal rate (eGDR – a marker for insulin resistance), ischaemic resting electrocardiogram, and abnormal ankle blood pressures to predict mortality in type 1 diabetes in the context of standard risk factors.

2 The study followed up 658 subjects with childhood-onset type 1 diabetes for 10 years.

3 The mortality hazard ratios and 95% confidence intervals associated with ischaemic ECG, the lowest quintile of eGDR, ankle brachial index (ABI) and ankle brachial difference (ABD) were only marginally less than those conveyed by pre-existing coronary artery disease or overt nephropathy.

4 eGDR in the lowest quintile, ischaemic ECG and ABD 75+, each increased mortality risk sevenfold.

5 Ischaemic ECG was a particularly strong mortality predictor among subjects free of baseline coronary artery disease or overt nephropathy.

6 HbA_{1c} was an independent mortality predictor in this study if serum creatinine was also in the model. The eGDR, which includes HbA_{1c}, was itself an independent mortality predictor if creatinine was not available, and an independent predictor of renal disease mortality.

7 Ischaemic ECG and eGDR were independent mortality predictors, together with duration of diabetes, coronary artery disease, overt nephropathy, non-high density lipoprotein cholesterol, and smoking history.

8 The authors therefore suggest that eGDR and ECG might be useful in the identification of patients at risk of type 1 diabetes.

9 The results support the use of eGDR, ischaemic ECG and ABI<0.8 in conjunction with ABD 75+ in identifying type 1 diabetics at increased risk of mortality.

Olson JC, Erbey JR, Williams KV, Becker DJ et al (2002) Subclinical atherosclerosis and estimated glucose disposal rate as predictors of mortality in type 1 diabetes. *Annals of Epidemiology* **12**: 331–7

'Ischaemic ECG was a particularly strong mortality predictor in subjects free of baseline coronary artery disease or overt nephropathy.'