Management & prevention of type 2 diabetes

Glitazones as second-line agents

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The dream was that an insulin sensitising drug would overcome the barrier posed by insulin resistance, up-regulate the action of endogenous insulin and abolish the need for adjuvant insulin therapy in type 2 diabetes.

Unfortunately, the reality falls some way short of the dream, but it does take us a step closer to realising it. A new class of insulin sensitisers – or at least two them, rosiglitazone and pioglitazone – do seem to offer people with type 2 diabetes (those at risk of developing diabetes and healthcare professionals who treat them) a new therapeutic option.

In the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study (summarised on right) 10.6 % of those treated with rosiglitazone in combination with diet and exercise interventions developed diabetes in the 3–5 years of follow-up. In comparison, 25 % of the placebo group developed the condition in this time. This represents a relative reduction in progression to diabetes of 62 % – the largest effect yet seen.

Some have complained that the absence of reductions in major vascular endpoints reduces the overall practical impact of these data. While this is so, the comments need to be put in context. In this population, with impaired glucose tolerance but relatively low absolute cardiovascular risk and studied over a relatively short time period, any reduction of cardiovascular events or mortality were unlikely to be detected. Positive effects on liver enzymes attributed to reduction in hepatic fat suggested a beneficial effect of this class of drugs on the hepatic manifestation of the metabolic syndrome. This is particularly reassuring given that the original drug in the class, troglitazone, was withdrawn because of fatal hepatotoxicity.

As monotherapy, in a double-act with a sulphonylurea or metformin, or as a triple combination with all three, rosiglitazone and pioglitazone seem to be safe and effective. The reduction in HbA_{1c} is modest but in line with that delivered by other oral hypoglycaemia agents: ~1 % (absolute). Additional data from A Diabetes Outcome Progression Trial (ADOPT; Kahn et al, 2006) suggest that the hypoglycaemia effect of the thiozolidienediones may be more sustained and durable than that delivered by other oral agents. On the grounds of cost and side-effects I agree with Nathan (2006) that metformin remains the first choice for both prevention and treatment; the glitazones, however, may now be the second-line agents of choice.

One of the key challenges identified by the DREAM study was that almost 25 % of participants were not taking their prescribed study medication at their final visit. This underlines the importance of maintaining life-long preventive interventions in an asymptomatic setting. Taken together with the DREAM washout data presented at the IDF conference in December 2006, where similar rates for new onset diabetes in the rosiglitazone and placebo groups (10.6 % and 9.7 % respectively) were reported, it is clear that dreaming is not enough: actually *taking* the tablets must be focussed on as an essential part of the deal.

Kahn SE, Haffer SM, Heise MA et al (2006) Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *New England Journal Medicine* **355**: 2427–43

Nathan DM (2006) Thiazolidinediones for initial treatment of type 2 diabetes? *New England Journal Medicine* **355**: 2477–80

The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators (2006) Effect of rosiglitazone on the frequency of diabetes in patients with impaired fasting glucose or impaired glucose tolerance: A randomized controlled trial. *Lancet* **368**: 1096–105

LANCET

Rosiglitazone reduces incidence of type 2 diabetes

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

1 The aim of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) investigation was to assess the ability of rosiglitazone to prevent incidence of type 2 diabetes in high-risk individuals.

2 The trial investigated 5269 people over 30 years of age who had impaired fasting glucose or impaired glucose tolerance for a median of 3 years. They were randomised to receive either rosiglitazone (8 mg/day) or placebo (2365 and 2634 participants, respectively).

3 By the end of the study 306 of the individuals taking rosiglitazone and 686 of those on placebo had reached the primary endpoint of diagnosis of diabetes or death ($P<0.0001$).

4 Normoglycaemia occurred in 1330 of the rosiglitazone group and 798 in the placebo group ($P<0.001$). Heart failure occurred in 14 (0.5 %) of those taking the drug, compared with 2 (0.1 %) of those taking placebo ($P=0.01$), however other CV outcomes were similar between groups.

5 The study found that rosiglitazone at a dose of 8 mg daily over a mean period of 3 years will significantly reduce the incidence of type 2 diabetes in high-risk individuals. The drug also increases the likelihood of regression to normoglycaemia in the investigated population.

6 The authors conclude that for individuals at high risk of diabetes, early administration of rosiglitazone can reduce the risk of death or type 2 diabetes by 60 %.

The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators (2006) Effects of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* **368:** 1096–105

DIABETOLOGIA

Coffee antioxidants incur benefits to drinkers

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

1 Drinking coffee has been linked to a lower risk of developing type 2 diabetes but studies have yet to link coffee consumption to CVD.

2 This paper reports on a study investigating whether overall mortality and mortality from CVD, CHD and stroke were influenced by levels of coffee consumption in Finnish people with type 2 diabetes.

3 Over six initial surveys, 52 166 people were contacted. Of these, 3837 met the inclusion criteria of type 2 diabetes, entitlement to reimbursement for anti-diabetic drugs and having fully completed the survey; and were not excluded from the trial due to previous CHD or stroke.

4 Questionnaires including questions on medical history, socioeconomic factors, physical activity, coffee, tea and alcohol consumption and smoking habits were issued. Trained nurses measured blood pressure, height and weight.

5 Adjusted hazard ratios decreased with increasing coffee consumption for total mortality ($P<0.001$ for trend), CVD mortality ($P=0.006$ for trend) and CHD mortality ($P=0.01$ for trend). There was no significant trend between coffee consumption and death from stroke.

6 Limitations include the lack of information regarding the duration and severity of diabetes, the degree of glucose control and medication used by each participant.

7 The author's suggest that the antioxidants in coffee effect several components of the glucose metabolism pathway and thus incur beneficial results upon the control of hyperglycaemia.

Bidel S, Hu G, Qiao Q, et al (2006) Coffee consumption and risk of total and cardiovascular mortality among patients with type 2 diabetes. *Diabetologia* **49**: 2618–26

DIABETIC MEDICINE

DISNs reduce diabetes bed occupancy

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

1 People with diabetes stay in hospital longer than those without diabetes and are frequently dissatisfied with inpatient care standards. There is pressure to reduce the proportion of beds occupied by patients with chronic diseases.

2 The authors measured whether appointment of a Diabetes Inpatients Specialist Nurse (DISN) could reduce excess bed occupancy by the diabetes population by improving quality of care.

3 In this study, 9.7% of participants had diabetes, but accounted for 12.4% of inpatient bed days. Most of this excess was due to longer stays by younger patients.

4 Per person with diabetes, there was a significant fall in the mean excess bed days following the introduction of a DISN (ANOVA $P=0.04$).

5 This data supports the introduction of DISNs.

Sampson MJ, Crowle T, Dhatariya K et al (2006) Trends in bed occupancy for inpatients with diabetes before and after the introduction of a diabetes inpatient specialist nurse service. *Diabetic Medicine* **23**: 1008–15

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

CIMT progression slowed by pioglitazone

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

1 Increased carotid intima-media thickness (CIMT) is associated with an increased CV risk.

2 In a long-term, randomised, comparator-controlled trial in the US the progression of CIMT was measured in 462 type 2 diabetes individuals administered pioglitazone (15–45 mg/d) or glimepiride (1–4 mg/d).

3 At 18 months the pioglitazone group's CIMT measurements from baseline were 0.013 mm thinner than those of the glimepiride group ($P=0.02$).

4 The authors suggest that over 18 months pioglitazone slowed CIMT progression and therefore incurred a CV benefit.

Mazzone T, Meyer PM, Feinstein SB et al (2006) Effect of Pioglitazone Compared With Glimepiride on Carotid Intima-Media Thickness in Type 2 Diabetes. *Journal of the American Medical Association* **296**: 2572–81

ANNALS OF INTERNAL MEDICINE

Good short-term efficacy and safety of inhaled insulin

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

1 The authors examined efficacy, safety and patient acceptability of inhaled insulin by means of a systematic literature review.

2 Sixteen open label, randomised, controlled trials incorporating 4023 participants with types 1 and 2 diabetes were included.

3 HbA_{1c} levels favoured the use of subcutaneous insulin over inhaled insulin, but by the same measure inhaled insulin showed benefits over oral agents.

4 Comparisons between groups using inhaled insulin and those using oral agents showed a higher proportion of participants with at least one hypoglycaemic episode.

5 Participants in all trials reported significantly higher satisfaction with inhaled insulin.

Cegiia L, Lau J, Pittas AG (2006) Meta-Analysis: Efficacy and Safety of Inhaled Insulin Therapy in Adults with Diabetes Mellitus. *Annals of Internal Medicine* **145**: 665–75

JOURNAL OF HYPERTENSION

Reductions in microalbuminuria and blood pressure with rosiglitazone therapy

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

1 In type 2 diabetes, hypertension and poor glycaemic control are risk factors for the development of microalbuminuria.

2 This study set out to discover whether metformin plus rosiglitazone reduces the above microalbuminuria risk factors with a greater significance than metformin plus glyburide.

3 The study design was double-blind and parallel-group, with 389 participants studied for 32 weeks.

4 Metformin plus rosiglitazone significantly reduced the urinary albumin:creatinine ratio by 22.7% from baseline ($P<0.01$). Metformin plus glyburide reduced the urinary albumin:creatinine ratio by 7.1% from baseline ($P=0.32$).

5 The difference between the two groups was a 19.5% reduction in favour of metformin plus rosiglitazone ($P=0.03$), despite similar improvements in glycaemic control.

6 Metformin plus rosiglitazone additionally significantly reduced systolic and diastolic ambulatory blood pressures ($P=0.01$, $P<0.01$, respectively), levels of C-reactive protein ($P<0.01$), plasminogen activator inhibitor-1 antigen and activity ($P=0.03$, $P<0.01$, respectively), von Willebrand factor ($P<0.01$) and fibrinogen ($P<0.01$) in comparison to metformin plus glyburide.

7 The authors conclude that the results could be attributable to rosiglitazone's anti-inflammatory effects.

Bakris GL, Ruilope LM, McMorn SO et al (2006) Rosiglitazone reduces microalbuminuria and blood pressure independently of glycemia in type 2 diabetes patients with microalbuminuria. *Journal of Hypertension* **24**:2047–55

DIABETIC MEDICINE

Low quality online type 2 information

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

1 The authors assert that conveying information about type 2 diabetes to those at high risk is a key step in slowing the diabetes epidemic.

2 An international list of 34 websites found to provide health-related information on diabetes were reviewed.

3 Four, or 11.8%, provided no information on the family association of type 2 diabetes, and 3 (8.8%) did not mention family history as a risk factor.

4 Only six, or 17.6% provided detailed information about the inheritance of type 2 diabetes and risk percentages.

5 On the websites included in the study, 9 (26.5%) mentioned ethnicity as a risk factor with reference to specific ethnicities and regions, while 8 (23.5%) discussed ethnicity but in less detail.

6 Seven websites (20.6%) did not supply any information about primary prevention of type 2 diabetes.

7 Of the 34 websites, 4 (11.8%) directly linked to preventative information, discussed this in terms of behaviour changes and specifically targeted the data and advice to high-risk groups.

8 Readability was not assessed as part of this investigation, but it was noted that most websites required a high school level of reading proficiency, which may need to be toned down to be accessible for the lay audience.

9 The findings of this study suggest that information provided via the Internet by diabetes organisations needs to be improved in order to convey more successfully the preventative options for type 2 diabetes and the hereditary aspect of the condition.

van Esch SCM, Cornel MC, Snoek FJ (2006) Type 2 diabetes and inheritance: what information do diabetes organizations provide on the Internet? *Diabetic Medicine* **23**: 1233–8

HEALTH AND QUALITY OF LIFE OUTCOMES

Both insulin glargine and exenatide improve patient-reported outcomes

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

1 The authors set out to investigate whether patient-reported outcomes, rather than clinical outcomes, varied between those prescribed insulin glargine and those taking exenatide.

2 Over 26 weeks data were collected from 228 people with type 2 diabetes taking, in addition to their oral medications, exenatide 5 mg BID for 4 weeks then 10 mg BID and 227 people with type 2 diabetes taking insulin glargine forced titration to fasting blood glucose target ≤5.5 mmol/l (in addition to their oral medications).

3 Both regimens significantly improved outcomes in all health outcomes measures except those relating to diabetes flexibility score, pain score, sensory score and cardiology score.

4 Despite a previously documented decrease in body weight associated with exenatide in comparison to insulin and an identified link between weight reduction and positive health outcomes, this trial showed no difference between the groups in patient-assessed health outcome instruments.

5 The authors hypothesise that the expected improved patient outcomes in the exenatide group was confounded by the increased number of injections required for this treatment, and the increased frequency of GI side-effects.

Secnik Boye K, Matza LS, Oglesby A et al (2006) Patient-reported outcomes in a trial of exenatide and insulin glargine for the treatment of type 2 diabetes. *Health and Quality of Life Outcomes* **4**: 80