THE LANCET

Acarbose: the STOP-NIDDM randomised trial

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

1 The STOP-NIDDM trial assessed the effect of acarbose in preventing or delaying the conversion of impaired glucose tolerance (IGT) to type 2 diabetes.

2 A total of 714 patients with IGT were given 100mg acarbose, and 715 controls received placebo, three times daily.

3 The primary endpoint of the study was the development of diabetes on the basis of a yearly oral glucose tolerance test.

4 Of those receiving acarbose, 32% developed diabetes, compared with 42% for the placebo group. Therefore, acarbose significantly increased the reversion of IGT to normal glucose tolerance. In addition, when acarbose was discontinued at the end of the trial, the incidence of diabetes in this group increased.

5 The most frequent side-effects of treatment with acarbose were flatulence and diarrhoea.

6 In summary, treatment with acarbose reduced the risk of progression to diabetes over 3.3 years by 25%. The risk was effectively reduced irrespective of age, sex and body mass index.

Chiasson J-L, Josse RG, Gomis R et al (2002) Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. The Lancet 359: 2072–7

Timely intervention could still prevent diabetes epidemic

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Publication of the STOP-NIDDM Study adds to the growing body of evidence that the predicted epidemic of type 2 diabetes is not inevitable and that timely intervention in high-risk individuals can significantly reduce risk of progression from impaired glucose tolerance (IGT) to type 2 diabetes.

Earlier prospective case-control studies from China (Eriksson and Lindegarde, 1991) and Scandinavia (Pan et al, 1997) compared the impact of lifestyle intervention on reducing the risk of progression from IGT to diabetes, but the studies were criticised. The charge was of selection bias, with those more likely to respond to diet and exercise choosing to undergo the active intervention.

STOP-NIDDM is the third large prospective RCT to establish that the risk of diabetes can be reduced by intervention. The Finnish Diabetes Prevention Study Group, the first large-scale prospective RCT, randomly assigned 522 middle-aged overweight subjects (172 men and 350 women, mean age 55 years, mean BMI 31) with IGT to either intervention or control groups (Tuomilehto et al, 2002). Each subject in the intervention group received individualised dietary counselling aimed at reducing weight and total and saturated fat intake, and increasing fibre intake and physical activity. Mean weight loss at the end of 1 year was 4.2kg in the intervention group and 0.8kg in the control group. The cumulative incidence of diabetes over 4 years was 11% in the intervention group and 23% in the control group, a reduction of 58%. The reduction in the incidence of diabetes was directly associated with lifestyle changes. Importantly, subjects in the intervention group met with a dietitian seven times during the first year and every 3 months thereafter; subjects also received individual advice on how to improve their physical fitness.

The North American Diabetes Prevention Program tested the power of lifestyle intervention (diet and exercise) or metformin (850mg bd) in a much larger but essentially similar clinical group (Diabetes Prevention Program Research Group, 2002). An identical 58% reduction in progression to diabetes was seen in the intervention group, compared with a 31% reduction those treated with metformin. The incidence of diabetes was 11, 7.8 and 4.8 cases per 100 person-years in the placebo, metformin and lifestyle groups, respectively. To prevent one case of diabetes during a period of 3 years, seven persons would have to participate in the lifestyle intervention program and 14 would have to receive metformin. This latest study of acarbose 100mg tds or placebo found a 25% reduction in progression to diabetes over 3.3 years in those treated with acarbose. After allowing for wash-out (and the effect of acarbose treating diabetes rather than preventing it) more patients in the acarbose group (47 of 306) progressed to diabetes than in the group first randomised to placebo (21 of 199). Thus, at the very least, acarbose treatment must be continued to maintain benefit, and subjects accepting this treatment simply initiate oral hypoglycaemic medication at an earlier stage of glucose intolerance. Acarbose, however, was effective irrespective of age, sex and BMI, and although a small amount of weight loss was achieved in the acarbose group (0.5kg), acarbose was still effective after adjustment for weight loss. It is possible that even more effective diabetes prevention could be acheived by combining lifestyle interventions with either metformin or acarbose.

Reducing the predicted epidemic of diabetes is such an attractive prospect, and such a potential gold mine, that drug companies are investing large sums in prospective studies testing the ability of modern hypoglycaemic and antihypertensive therapies to delay the progression to diabetes. NAVIGATOR, the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcome TRial, will test the power of nateglinide and/or valsartan to prevent diabetes and adverse cardiovascular outcomes in subjects with IGT. The study is a 2X2 factorial design and aims to recruit 7500 patients in 40 countries.

DREAM, the Diabetes REduction Assessment with ramipril and rosiglitazone Medication trial, follows a similar design but trials the utility of thiazolidienedione rosiglitazone and the ACE inhibitor ramipril or both.

These studies, similar to the STOP-NIDDM, might prove successful, but offer only the prospect of using large pharmacological sledgehammers to crack the diabetes nut. In the trials to date, lifestyle intervention delivers surer, safer, more effective and more efficient diabetes prevention than drugs. But the lifestyle interventions proven to deliver are systematic, intensive and supported with the study participants receiving detailed, individualised counselling. The challenge, in the window of opportunity that remains, is to develop an infrastructure that facilitates access to the support necessary to initiate and sustain the behaviour change that delivers diabetes prevention.

Chaisson JL, Josse R, Gomis R et al (2002) Acarbose for prevention of type 2 diabetes: the STOP-NIDDM randomised trial. The Lancet 359: 2072–7

Eriksson KF, Lindegarde F (1991) Prevention of type 2 (non-insulin dependent) diabetes by diet and exercise: the 6 year Malmo feasibility study. Diabetologia 34: 891–8

Pan XR, Li GW, Hu YH et al (1997) Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. Diabetes Care 20: 537–44

Tuomilehto J, Lindstrom J, Eriksson JG et al (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. New England Journal of Medicine 344: 1343–50

Diabetes Prevention Program Research Group (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. New England Journal of Medicine 346: 393–403

'Low levels of highly phosphorylated IGFBP-1 closely correlate with macrovascular disease and hypertension.'

Low IGFBP-1 linked to macrovascular disease in diabetes

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

1 The actions of insulin-like growth factor (IGF) are largely regulated by IGF-binding proteins (IGFBPs). The status of one of these proteins, IGFBP-1, was assessed in 160 patients with type 2 diabetes.

2 Total IGFBP-1 (which is mainly highly phosphorylated) was lower in subjects with known macrovascular disease than in patients with no vascular pathology.

3 For every decrease of 2.73μg/l in IGFBP-1, there was a 43% increase in the chance of the subject having macrovascular disease.

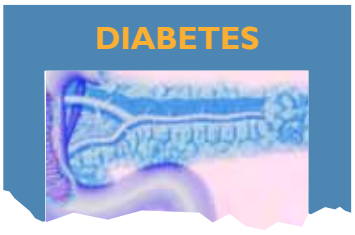
4 The levels of total IGFBP-1 were higher in subjects treated with insulin alone than in subjects in any other group.

5 The level of IGFBP-1 was also found to correlate negatively with systolic blood pressure, diastolic blood pressure, mean arterial pressure, body mass index, triglyceride concentrations, circulating insulin C-peptide and insulin levels.

6 Levels of nonphosphoryated or lesser-phosphorylated IGFBP-1 were unrelated to macrovascular disease or hypertension, but did correlate positively with fasting glucose concentrations.

7 In conclusion, low levels of highly phosphorylated IGFBP-1 closely correlate with macrovascular disease and hypertension, whereas levels of lesser-phosphorylated IGFBP-1 are associated with glycaemic control.

Heald AH, Siddals KW, Fraser W et al (2002) Low circulating levels of insulin-like growth factor binding protein-1 (IGFBP-1) are closely associated with the presence of macrovascular disease and hypertension in type 2 diabetes. Diabetes 51: 2629–36



Type 2 diabetes and ACE gene polymorphisms

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

1 This study set out to examine the role of an ACE gene insertion/deletion polymorphism in type 2 diabetes.

2 This polymorphism is characterised by the presence or absence of a 287-bp sequence in intron 16, which is suggested to be associated with coronary heart disease and nephropathy in people with type 2 diabetes.

3 A case-control association study was carried out among 132 couple-pairs from northern China. Each pair comprised a type 2 diabetic proband and his/her nondiabetic spouse.

4 Genotype frequencies for II, ID and DD were 39.8, 39.8 and 20.3, respectively, in the case group, and 44.8, 44.8 and 10.4% in the control group.

5 The higher prevalence of the DD genotype in the case group compared with the control group was significant, and suggested that this genotype is associated with an increased susceptibility to type 2 diabetes.

Feng Y, Niu T, Xu X et al (2002) Insertion/deletion polymorphism of the ACE gene is associated with type 2 diabetes. Diabetes 51: 1986–8

'Post-challenge glucose concentrations were inversely related to birth weight and length in men, and inversely related to birth weight and ponderal index in women...'

Higher birth size may protect against glucose intolerance

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

1 This study investigated the link between birth size and adult glucose intolerance.

2 The subjects comprised a genetically homogeneous population with higher birth weight and lower prevalence of type 2 diabetes: 2362 men and 2286 women, aged 33–65 years.

3 Post-challenge glucose concentrations were inversely related to birth weight and length in men, and inversely related to birth weight and ponderal index in women, especially in those with a higher body mass index.

4 In men, the prevalence of dysglycaemia was lower with increasing weight and length at birth, but had no relation to ponderal index.

5 For women, there was no linear trend for dysglycaemia in relation to size at birth, but the relation with birth length was U-shaped.

6 It therefore appears that higher birth weight and length can protect against glucose intolerance.

Birgisdottir BE, Gunnarsdottir I, Thorsdottir I et al (2002) Size at birth and glucose intolerance in a relatively genetically homogeneous, high-birth weight population. American Journal of Clinical Nutrition 76: 399–403

ARCHIVES OF INTERNAL MEDICINE

Treating diabetic dyslipidaemia with once-daily niacin

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

1 The efficacy and safety of once-daily extended-release (ER) niacin was evaluated in patients with diabetic dyslipidaemia.

2 It had been suggested that such treatment increases fasting blood glucose levels. This study aimed to question this, and if such an increase was observed, to assess whether it could be adequately controlled by adjusting the concomitant antidiabetic pharmacotherapy.

3 A total of 148 patients received either placebo, or 1000 mg/day or 1500 mg/day ER niacin for 16 weeks. Of these, 69 patients were also receiving therapy with statins.

4 Treatment with niacin resulted in an increase in high-density lipoprotein cholesterol levels in a dose-dependent manner, and a reduction in triglyceride levels.

5 Glycosylated haemoglobin levels were measured at baseline and week 16. Changes in HbA_{1c} levels were almost indistinguishable between the placebo and 1000 mg/day ER niacin groups; there was a small increase in the 1500 mg/day ER niacin group.

6 These data show that lower doses of ER niacin (1000–1500 mg/day) are effective and safe in the management of dyslipidaemia associated with type 2 diabetes, whether given alone or with a statin.

7 In addition, changes in glycaemic control were minimal, and, where evident, were successfully managed by adjusting the antidiabetic pharmacotherapy.

8 Rates of adverse event rates other than flushing were similar for the niacin and placebo groups. No hepatotoxic effects or myopathy were observed.

Grundy SM, Lena Vega G, McGovern ME et al (2002) Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes. Archives of Internal Medicine 162: 1568–76

'Treatment with niacin increased high-density lipoprotein cholesterol levels in a dose-dependent manner.'

THE AMERICAN JOURNAL OF MEDICINE

Comparison of risk factor management in type 2 diabetes

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

1 Hyperglycaemia management was compared with the management of cardiovascular risk factors – hypertension and hypercholesterolaemia – in patients with type 2 diabetes.

2 The care received by 601 patients was assessed over an 18-month period.

3 It was found that patients were less likely to have their cholesterol levels measured than their HBA_{1c} levels or their blood pressure.

4 The proportion of patients receiving any drug therapy was greater for above-goal HbA_{1c} than for above-goal systolic blood pressure or low-density lipoprotein (LDL) cholesterol.

5 Similarly, patients whose HbA_{1c} levels were above the treatment goal were more likely to receive greater-than-starting-dose therapy, compared with those who had above-goal systolic blood pressure and LDL cholesterol levels.

6 Hypercholesterolaemia and hypertension were managed less aggressively than hyperglycaemia. Given the prevalence of cardiovascular disease in patients with type 2 diabetes, screening and therapy need to be increased for these factors.

7 In summary, the study found significant differences in the relative effectiveness of management across the major domains of metabolic control in diabetes care.

8 However, there were no differences between the Diabetes Center and general medicine clinics in the effectiveness of hypertension management or hypercholesterolaemia management.

Grant RW, Cagliero E, Murphy-Sheehy P et al (2002) Comparison of hyperglycemia, hypertension, and hypercholesterolemia management in patients with type 2 diabetes. The American Journal of Medicine 112: 603–9

'Patients were less likely to have their cholesterol levels measured than their HbA_{1c} levels or their blood pressure.'