Basic science

Treating type 2 diabetes requires a combined effort

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It is now an accepted fact that tight glycaemic control in patients with type 2 diabetes can reduce the incidence and severity of chronic complications. Current pharmacotherapy to control hyperglycaemia includes sulphonylureas (which increase islet insulin release), metformin (which reduces hepatic glucose production), thiazolidinediones (which enhance insulin action) and α-glucosidase inhibitors (which interfere with gut glucose absorption). These antidiabetic agents used in isolation often fail to achieve the near-normal glycaemic control targets set out in the current treatment guidelines for type 2 diabetes.

The article by Van Gaal and De Leeuw suggests that good glycaemic control ($HbA_{1c} < 7\%$) can only be achieved in large numbers of patients if a combination treatment regimen is used. Indeed, available evidence indicates that combined therapy may be able to prevent the progressive worsening of diabetes in patients who have become refractory to treatment with oral hypoglycaemic agents (OHAs), despite good early responses. This prevention of so-called secondary failure in type 2 diabetes must be a major goal in controlling hyperglycaemia and delaying or averting chronic complications.

The current article provides a detailed account of both the rationale and options for combination therapy and highlights the importance of controlling both postprandial and fasting hyperglycaemia. The worsening of insulin resistance that occurs as a result of poorly controlled postprandial hyperglycaemia and its subsequent role as an independent risk factor for vascular complications is of particular concern.

The authors describe a number of new approaches to combination therapy including the use of new, rapid-acting ß-cell stimulating agents like nateglinide and repaglinide with both metformin and the thiazolidinediones. An approach using nateglinide or repaglinide and sulphonylureas was not, however, recommended.

The overall conclusion from Van Gaal and De Leeuw appears to be that early combination therapy is indicated whenever there is a high rate of secondary failure on monotherapy, irrespective of the actual agent being used.

Type 2 diabetes is a heterogeneous disorder involving a common group of closely linked clinical features and any therapy should seek to target all or as many of these symptoms as possible. It is extremely unlikely therefore, that any single therapeutic agent will be able to effectively manage the entire glycaemic risk in type 2 diabetes, but this may be achievable with early more imaginative combination therapy.

DIABETES

Guidelines for intervention trials in type 1 diabetes

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

1 Intervention trials in newly diagnosed patients with type 1 diabetes vary considerably in terms of entry criteria, trial design and duration, and outcome measures.

2 This article describes the issues pertaining to trial variables and suggests ways of standardising protocols for phase I and II intervention trials in newly diagnosed patients.

3 For example, the authors suggest that recognised criteria (such as the American Diabetes Association criteria) be used to make a diagnosis, and that treatment should be evaluated for at least 2 years.

4 Standardisation of islet autoantibody assays and of the intravenous glucose tolerance test for measuring first-phase insulin response has been a major advance, which has allowed disease risk stratification to be done among relatives.

5 Adoption of standardised protocols would permit comparative and pooled data analysis and facilitate evaluation of potential therapies.

Greenbaum CJ, Harrison LC (2003) Guidelines for intervention trials in subjects with newly diagnosed type 1 diabetes. *Diabetes* **52**: 1059–65

DIABETOLOGIA

Combination therapy for type 2 diabetes

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

1 Guidelines for the management of type 2 diabetes now set aggressive targets of HbA_{1c} <7%, with the aim of reducing the risk of microvascular and macrovascular complications. Such challenging targets suggest that clinicians need to re-evaluate their treatment strategies.

2 This article presents the rationale and options for combination therapy in the treatment of patients with type 2 diabetes.

3 Currently used oral antidiabetic agents such as sulphonylureas, biguanides and the thiazolidinediones target fasting hyperglycaemia and have limited effects on postprandial glycaemia.

4 There is evidence to suggest that the combination of oral antidiabetic agents with complementary mechanisms of action is highly effective in achieving and maintaining tight glycaemic control.

5 Any effective combination therapy should improve clinical symptoms, quality of life, restore euglycaemia both in the fasting and postprandial state without inducing hypoglycaemia, and prevent or delay the development of long-term vascular complications.

6 New short-acting enhancers of insulin secretion, such as repaglinide and nateglinide, could be used in combination with insulin sensitisers.

7 Any combination therapy should be based on an understanding of type 2 diabetes and the complementary pharmacological action of the antidiabetic agents used.

Van Gaal LF & De Leeuw IH (2003) Rationale and options for combination therapy in the treatment of type 2 diabetes *Diabetologia* **46** (suppl): M44–M50

'The ability to culture insulin-producing pancreatic islet cells from embryonic stem cells holds great promise for the cure of type 1 diabetes'

'Consideration of antioxidants as adjunct therapy in type 2 diabetes is warranted because of reports of elevated markers of oxidative stress in such patients.'

JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Potential of stem cell therapy

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

1 This is a review of the recent developments in the use of stem cells as therapeutic agents in chronic disease, including diabetes.

2 The ability to culture insulin-producing pancreatic islet cells from embryonic stem cells holds great promise for the cure of type 1 diabetes.

3 However, it is difficult to induce embryonic stem cells to differentiate into a specific lineage.

4 Purification of a single cell type from the initial mixed population is also difficult.

5 Ethical, religious, and political issues associated with derivation and use of embryonic stem cells have not been fully resolved and remain stumbling blocks that impede further research.

Henningson CT, Stanislaus M, Gewirtz AM (2003) Embryonic and adult stem cell therapy *Journal of Allergy & Clinical Immunology* **111**: 745–53

DIABETES

Glucose toxicity in type 2 diabetes

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

1 A possible reason for why patients with type 2 diabetes, who initially respond to diet and oral hypoglycaemic agents, usually relapse into hyperglycaemia is presented.

2 The glucose toxicity theory proposes that continual exposure to modest increases in blood glucose over a long period of time could have adverse effects on ß-cells.

3 The authors suggest that the characteristic decreases in insulin synthesis and secretion are caused by decreased insulin gene expression. PDX-1, a critical regulator of promotor activity, is absent in glucotoxic islets.

4 Chronic oxidative stress is proposed as an important mechanism for glucose toxicity.

5 Consideration of antioxidants as adjunct therapy in type 2 diabetes is warranted because of reports of elevated markers of oxidative stress in such patients.

Robertson RP, Harmon J, Tran PO, Tanaka Y, Takahashi H (2003) Glucose toxicity in ß-cells: type 2 diabetes, good radicals gone bad, and the gluctathione connection *Diabetes* **52:** 581–87

PROGRESS IN BIOPHYSICS AND MOLECULAR BIOLOGY

Are K_{ATP} channels a potential target for new drugs?

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

1 This is a review of the physiological and pathophysiological roles of ATP-sensitive potassium (K_{ATP}) channels.

2 K_{ATP} channels are found in many tissues, including pancreatic islet cells, heart, skeletal muscle, vascular smooth muscle and brain, where they have crucial roles in various cellular functions.

3 Based on studies of K_{ATP} channel knockout mice and transgenic mice, as well as naturally occurring mutations in humans, it is now clear that K_{ATP} channels as metabolic sensors, are critical in protective mechanisms such as hyperglycaemia, hypoglycaemia, ischaemia, and hypoxia.

4 K_{ATP} channel subunit-null mice and various transgenic mice expressing a mutant K_{ATP} channel subunit should be useful for further elucidation of the pathophysiological roles of K_{ATP} channels in various metabolic and cardiovascular disorders and for the development of novel drugs targeting K_{ATP} channels.

Seino S, Miki T (2003) Physiological and pathophysiological roles of ATP-sensitive K^+ channels. *Progress in Biophysics & Molecular Biology* **81**: 133–76

DIABETOLOGIA

Enhancing islet transplantation

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

1 Use of islet transplantation offers hope for the complete cure of patients with type 1 diabetes. However, in previous studies, two to four pancreas donors were required to achieve a sufficient islet mass.

2 The aim of this study was to increase the expression of the insulin gene in transplanted islets in an attempt to reduce the number of potential donors required.

3 A replication defective adenovirus was used to deliver the human proinsulin gene (Ad-Ins) to isolated human islets. The function of Ad-Ins transduced human islets was compared with islets transduced with a control vector (Ad-lacz).

4 Ad-Ins transduced islets produced two to three times more insulin than normal islets or those infected with Ad-lacz.

5 After transplantation, Ad-Ins transduced islets normalised the blood glucose of diabetic immunodeficient NOD-Scid mice. Less than half as many Ad-Ins islets were required for reversal of diabetes than when normal islets were transplanted

6 This approach could provide a solution to the shortage of organs by supplying islet tissue until other strategies such as stem-cell derivation of ß-cells or xenogeneic sources of islet issue can be refined.

Deng S, Vatamaniuk M, Lian M-M et al (2003) Insulin gene transfer enhances the function of human islet grafts *Diabetologia* **46**: 386–93