Basic science

DIABETES

β-cell apoptosis decreases ß-cell mass in diabetes

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

1 Some studies suggest that a decrease in β-cell mass contributes to impaired insulin secretion.

2 Pancreatic tissue from 124 autopsies was examined: 91 obese cases (41 type 2 diabetic, 15 impaired fasting glucose [IFG] and 35 non-diabetic) and 33 lean cases (16 type 2 diabetic; 17 non-diabetic).

3 Relative β-cell volume was increased in obese vs lean non-diabetic cases by neogenesis. Obese subjects with IFG and type 2 diabetes had a 40% and 63% deficit, and lean cases with type 2 diabetes had a 41% deficit in relative β-cell volume compared with non-diabetic and lean cases, respectively.

4 The frequency of β-cell replication was low in all cases and was similar between groups.

5 Neogenesis was comparable in obese type 2 diabetic, IFG or non-diabetic subjects and in lean type 2 diabetic or non-diabetic subjects.

6 The frequency of β-cell apoptosis was increased 10-fold in lean and 3-fold in obese cases of type 2 diabetes compared with respective non-diabetic controls.

7 The authors conclude that β-cell mass is decreased in type 2 diabetes and that this is caused by increased β-cell apoptosis. Therapeutic approaches could possibly be designed to arrest apoptosis.

Butler AE, Janson J, Bonner-Weir S et al (2003) ß-cell deficit and increased ß-cell apoptosis in humans with type 2 diabetes. *Diabetes* **52**: 102–10

Type 2 diabetes: a question of balance?

Professor Adrian Bone, Head of Research, School of Pharmacy & Biomolecular Sciences, University of Brighton

Failure to maintain a sufficient mass of properly functioning β cells is a determining factor in the development of both type 1 and type 2 diabetes. The massive decline in β-cell mass in type 1 diabetes, which occurs as a result of the selective autoimmune destruction of the insulin-producing β cells is well established.

Type 2 diabetes, however, is thought to be characterised predominantly by β-cell dysfunction rather than β-cell loss. The paper by Butler et al reports, for the first time, major alterations in β-cell mass in a large number of people with type 2 diabetes who were studied at autopsy. This important study demonstrates just what can be achieved when an integrated clinical and basic science approach is used to elucidate the disease processes underlying a complex multifactorial condition such as type 2 diabetes. It is the availability of well-preserved pancreatic autopsy material combined with reliable clinical information on matched groups of patients that makes this research unique.

The authors have performed an in-depth investigation of β-cell mass by examining the balance between pathways of β-cell formation and death in both obese and lean humans with type 2 diabetes compared with age/weight-matched controls without diabetes. It is clearly demonstrated that the β-cell mass is decreased in lean and obese patients with type 2 diabetes, and this loss occurs irrespective of treatment by diet, oral hypoglycaemic agents or insulin. Furthermore, the mechanism for this β-cell deficit is a marked increase in β-cell apoptosis since both β-cell neogenesis and replication remain essentially unaffected.

These findings could have major implications for the treatment of type 2 diabetes. Thus it may be possible to prevent the progressive decline in β-cell mass leading to secondary failure by inhibiting apoptosis and restoring the balance of β-cell homeostasis. More interesting, perhaps, is the suggestion by the authors of the possibility of restoring β-cell mass in patients with established diabetes, given that the mechanisms for new islet formation appear to remain intact.

DIABETOLOGIA

Current treatment options for diabetic retinopathy

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

1 Retinopathy is the most frequently reported chronic complication of diabetes and is well understood. This article reviews current knowledge of the condition.

2 Powerful tools that can delay the onset and progression of diabetic retinopathy by achieving near-normal blood glucose and blood pressure levels are available.

3 Laser photocoagulation has proved very effective when retinopathy has progressed to a sight-threatening level.

4 However, retinopathy is still a major cause of blindness, and diabetes-related visual loss does not seem to have decreased in the developed world.

5 Screening for retinopathy would be the most cost-effective medical procedure to prevent its progression but there seems to be a lack of interest in its implementation by healthcare systems.

6 The future looks more optimistic, however, with the development of improving clinical skills and technology. Pathogenesis-targeted forms of treatment are being developed.

Porta M, Bandello F (2002) Diabetic retinopathy: a clinical update. *Diabetologia* **45**: 1617–34

'Fas-mediated apoptosis contributes significantly to the destruction of insulin-producing cells and the development of diabetes.'

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

Fas is significant in the development of diabetes

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

1 Fas is a death receptor involved in apoptosis and is expressed on insulin-producing β cells. But whether Fas contributes to the development of autoimmune diabetes is uncertain.

2 Non-obese diabetic mice developing spontaneous autoimmune diabetes (NOD) mice were generated with β-cell specific expression of a dominant- negative point mutation in a death domain of Fas (Fas^{cg}).

3 Spontaneous diabetes was delayed in NOD mice expressing Fas^{cg}.

4 Fas-mediated apoptosis contributes significantly to the destruction of insulin-producing cells and the development of diabetes.

Savinov AY, Tcherepanov A, Green AE, Flavell RA, Chervonsky AV (2002) Contribution of Fas to diabetes development. *Proceedings of the National Academy of Sciences* **100**(2): 628–32

DIABETES

Alginate barrier protects against xenorejection

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

1 The availability of human pancreatic tissue for islet transplantation is limited. Use of xenogeneic islets from pigs could be a potential alternative, but these are difficult to isolate.

2 In this study, microencapsulated neonatal pancreatic cell clusters (NPCCs) from pigs were transplanted into the peritoneal cavity of 32 streptozocin-induced diabetic B6AF1 mice.

3 Encapsulated NPCCs differentiated into ß cells and reversed the high blood glucose levels in immunocompetent mice without immunosuppression for >20 weeks.

4 Neonatal porcine pancreas could provide large numbers of insulin-producing cells for transplantation.

Omer A, Duvivier-Kali VF, Trivedi N, Wilmot K, Bonner-Weir S, Weir GC (2003) Survival and maturation of microencapsulated porcine neonatal pancreatic cell clusters transplanted into immunocompetent diabetic mice. *Diabetes* **52**: 69–74

DIABETOLOGIA

Insulin resistance associated with β-cell dysfunction

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

1 By the time hyperglycaemia develops, reductions in both insulin sensitivity and β-cell function have already occurred. This review focuses on the importance of these conditions in the pathogenesis of type 2 diabetes.

2 Obesity seems to be an important factor in the development of insulin resistance. In the presence of a genetic propensity to β-cell dysfunction, this leads to alterations in glucose tolerance.

3 Insulin sensitivity is influenced by a number of factors: genetics, age, acute exercise, physical fitness, dietary nutrients, medications, obesity and body fat distribution, with central adiposity and specifically intra-abdominal fat being an important factor.

4 Beta-cell dysfunction is evident in type 2 patients with diabetes. It seems that β-cell function is diminished early in the disease process and declines progressively as glucose tolerance decreases.

5 There is a hyperbolic relationship between insulin sensitivity and insulin secretion. A feedback loop governs the interaction between the β-cell and the insulin-sensitive tissues.

6 Greater understanding of the relative roles of insulin resistance and β-cell dysfunction in type 2 diabetes will help advances in genetics and in treating and preventing type 2 diabetes.

Kahn SE (2003) The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. *Diabetologia* **46**: 3–19

'There is a hyperbolic relationship between insulin sensitivity and insulin secretion. A feedback loop governs the interaction between the β-cell and the insulin-sensitive tissues.'

THE LANCET

New subtype of autosomal dominant diabetes

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

1 ATP-sensitive potassium (K_{ATP}) channels are major regulators of glucose-induced insulin secretion in pancreatic β cells.

2 This study assesses the effects of a dominant mutation (E1506K) in the K_{ATP} subunit (SUR1) of patients with congenital hyperinsulinaemia in a large Finnish pedigree.

3 Tests of glucose tolerance, insulin secretion and insulin sensitivity were carried out in 11 people heterozygous for the E1506K mutation and 19 controls without diabetes.

4 Four people heterozygous for the SUR1 E1506K mutation had diabetes, five had impaired glucose tolerance, one had impaired fasting glucose, and one had normal glucose tolerance.

5 Heterozygous E1506K substitution in the SUR1 gene causes congenital hyperinsulinaemia in infancy, loss of insulin secretory capacity in early adulthood, and diabetes in middle-age.

6 This variant represents a new subtype of autosomal dominant diabetes.

Huopio H, Otonkoski T, Vauhkonen I, Reimann F, Ashcroft FM, Laakso M (2003) A new subtype of autosomal dominant diabetes attributable to a mutation in the gene for sulfonylurea receptor 1. *Lancet* **361**: 301–07