

## Improving Glycaemic Control – A Mandatory Action Calling for Effective Therapeutic Management

a report by

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Diabetes mellitus is becoming one of the most common diseases in the world. The number of people with diabetes is estimated to double in the next 20 years, reaching 350 million affected people by 2025 (see *Figure 1*). This will be accompanied by an increased number of diabetic patients with long-term complications, causing a phenomenal increase in the health costs of several countries. At present there is no cure for diabetes, but many exciting steps have been taken in the past ten years, making the future of diabetic patients look cautiously optimistic.

### Prevention of Diabetes

Along with advances in the treatment of hyperglycaemia and associated metabolic disturbances and diabetic complications, a future challenge will be to design preventative measures that may lower the incidence of diabetes in the world. Recent studies have highlighted the importance of lifestyle modification in preventing diabetes in high-risk individuals. Lifestyle modifications also provide beneficial effects on the entire cardiovascular risk profile. However, long-term adherence to such interventions and feasibility in a non-trial setting remain potentially limiting factors to widespread implementation.

Pharmacological therapy may represent an interesting option. Positive results have been obtained with acarbose, metformin and glitazones, the latter suggesting that these compounds may actually modify the natural history of the disease. However, the data are not definitive and no single agent can currently be recommended for diabetes prevention. Effective treatment of obesity is also a valid opportunity, as suggested by early studies.

The approach for effective prevention of type 1 diabetes is different. As the possibility of desensitising the immune system with small doses of insulin in the pre-hyperglycaemic phase has been dismissed, an innovative solution may arise from genetic and immunosuppressive advances.

Transgenic expression of several proteins and transcription factors provides several theoretical

opportunities. Expression of the pro-insulin gene in the thymus results in the disappearance of pro-insulin reactive T-cells, preventing experimental type 1 diabetes. Similar results have been obtained with injection of islets or putative autoantigens, such as insulin B-chain or glutamate decarboxylase 65 (GAD65) proteins, in the thymus. Thus, injection of autoantigens in the thymus of high-risk individuals may represent an option, although more work is necessary to verify the efficiency of such a strategy.

Antigen-presenting cells (APC) are also the subject of much research as they are responsible for uptake and presentation of antigens to T-cells. APC residing in pancreas were then considered a target for gene therapy in type 1 diabetes. Genetic modification of APC in pancreas allows for local production of molecules that may interfere with activation and processing of antigens, limiting upregulation of adhesion molecules and interaction of APC-secreted factors with target cells. Gene transfer technology has been employed to ensure expression of interleukin (IL)-4 or modification of class I major histocompatibility complex (MHC) gene expression in pancreatic beta cells to prevent autoimmunity in non-obese diabetic mice. Optimisation of insulin secretion from residual beta cells was also achieved by gene transfer technology. Finally, transfer of the anti-apoptotic gene bcl-2 in beta cells may prevent apoptosis and autoimmune beta cell destruction or destruction of transplanted beta cells.

Pancreatic beta cells are characterised by poor growth capacity. Although pancreatic stem cells are likely to be found in the pancreatic ductal epithelium, islet neogenesis in diabetic animals was not observed. However, stimulation of beta cell neogenesis and replication of residual beta cells might provide an effective strategy preventing type 1 diabetes. This goal is currently pursued via activation or insertion of pyruvate dehydrogenase complex protein X 1 (PDX1) into progenitor cells. Other genes include members of the regenerating gene (REG) family, also shown to be involved in beta cell regeneration in animal models.

## New Therapies for Type 2 Diabetes

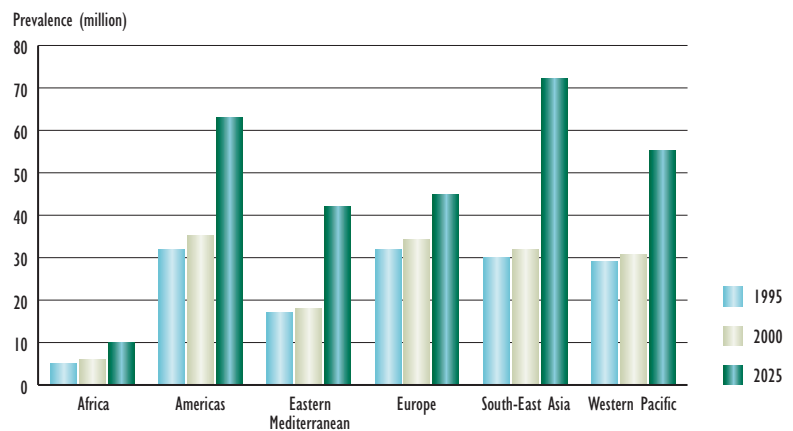
For decades, treatment of type 2 diabetes has been limited to sulfonylureas and metformin. Recent years, however, have consigned new therapeutic options to the endocrinologist. These new therapeutic opportunities allow the endocrinologist to tackle, possibly in a more effective manner, the two main pathogenetic factors of type 2 diabetes: insulin resistance and defective insulin secretion. The new pharmacological options reflect significant advances in the understanding of the physiological regulation of insulin secretion and action. With respect to insulin secretion, major advances have been made thanks to the comprehension of the role of the incretins in determining the surge of insulin secretion after the ingestion of a meal. The crucial role of glucagon-like peptide 1 (GLP-1) has been recognised. Unfortunately, the native hormone has limited use in pharmacology due to its rapid degradation by dipeptidyl enzymes (DPP-IV).

The problem has been overcome with the discovery of GLP-1 receptor agonists (exenatide) and specific DPP-IV inhibitors. While exenatide is already available for the treatment of type 2 diabetic patients, the DPP-IV inhibitors are in an advanced phase of development. The former requires subcutaneous injection, while the latter is administered *per os*. Both treatments potentiate glucose-mediated insulin secretion, causing improvement in glycaemic control at low risk of hypoglycaemia. They also have important associated effects, including reduced gastric motility, suppressed glucagon levels, reduced appetite and, at least in animal studies, increased beta cell mass.

Recently, pramlintide, a synthetic analogue of amylin (a hormone co-secreted with insulin by the pancreatic beta cells), has been introduced into the antidiabetic pharmacopoeia. The anti-hyperglycaemic action of the compound is due to inhibition of glucagon, modulation of gastric emptying and appetite suppression.

The introduction of peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) agonists (rosiglitazone and pioglitazone) has opened a new chapter in terms of not only glucose-lowering therapy, but also the understanding of physiology. These compounds not only improve insulin sensitivity, but also exert a pleiotropic action involving preservation of beta cell and cardiovascular protection. These actions include anti-inflammatory, vasoactive and anti-atherogenic properties as well as beneficial effects on lipid profile and arterial blood pressure. The growing knowledge of the physiological action of PPARs and the recognition

Figure 1: Worldwide Prevalence of Type 2 Diabetes in 1995, 2000 and 2025 (Estimated)



Source: King H et al., *Diabetes Care* (1998);21(9): pp. 1,414–1,431.

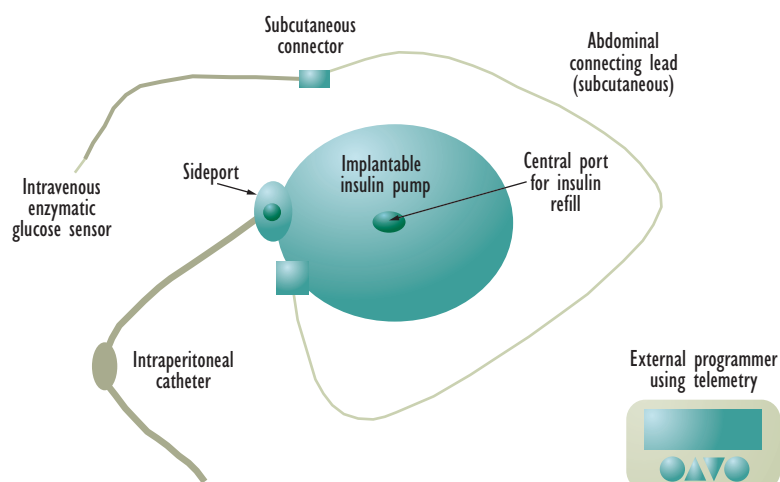
that PPAR- $\alpha$  is the pharmacological target of fibrates have prompted the pharmaceutical industry to search for dual PPAR- $\gamma/\alpha$  in the attempt to provide a more comprehensive metabolic control, including glucose-lowering therapy, triglyceride reduction and high-density lipoprotein (HDL) cholesterol increase. These drugs are in an advanced stage of development, but require careful assessment of the risk/benefit ratio.

Better understanding of the mechanisms responsible for insulin signalling and glucose metabolism are likely to identify novel targets for treatments aiming at improving insulin sensitivity in type 2 diabetic patients. Thus, inhibitors of phosphatase, such as oligo-elements (i.e. vanadium), or of phosphoinositol-3-kinase may provide alternative options for the modulation of insulin action in insulin-dependent tissues.

Activation of glycogenesis or suppression of glycogenolysis and gluconeogenesis and reduction in hepatic glucose output are all potential objectives for specific therapies. This approach may take advantage of agents capable of modulating the activity of the enzymes directly or indirectly through modulation of hormones, for instance glucagon.

Reduction in body weight is of primary importance given the deleterious effect of excessive adipose tissue, particularly when accumulated in the abdominal and visceral area and in ectopic tissues (muscle and liver). The cannabinoid receptor 1 (CB1) inhibitor rimonabant presents a promising opportunity because not only may its central action reduce appetite and therefore favour weight loss, but the cannabinoid receptors also appear to be expressed in tissues other than the central nervous system (CNS). On account of these peripheral receptors, rimonabant may exert a specific action on metabolic disturbances of the obese type 2 diabetic patient.

Figure 2: Artificial Pancreas



Source: Renard E, Curr. Opin. Pharmacol. (2002);2(6): pp. 708–716.

### Beta Cell Replacement – Pancreas or Islets Transplantation, Stem Cells and Artificial Pancreas

Type 1 diabetes is characterised by a loss of beta cells due to autoimmune insult, and insulin replacement is mandatory for survival and prevention of both acute and chronic complications. This is usually achieved by subcutaneous injection of insulin. Over the past years, several modifications to insulin preparations have been made in order to provide better glycaemic control in the basal state and after ingestion of meals, the last advance being represented by the short- (lispro and aspart) and long-acting (glargine and detemir) insulin analogues.

Alternative routes of administration have been sought for a long time. These include transmucosal, oral and nasal administration. However, pulmonary absorption of insulin appears to be much closer to approval. Both powder and liquid insulin have been developed that can be transferred, through inhalation, to the alveoli to ensure rapid and effective absorption.

#### Pancreas or Islets Transplantation

The final objective in the treatment of type 1 diabetes is the restoration of endogenous insulin sources. At present, only pancreas transplantation can achieve insulin independence. With the introduction of more effective and safer immunosuppressive therapy, the success of whole-organ transplantation has improved dramatically. During the last decade, patient and graft survival were 91% and 75% at one year, 88% and 72% at two years and 85% and 67% at three years, respectively. Further improvement in the risk/benefit ratio of chronic immuno-suppressive therapy will be

welcome as it will provide better selectivity in the prevention of graft rejection.

An alternative option to whole-organ transplant is the intra-hepatic engraftment of isolated pancreatic islets. The procedure is less invasive but remains much less used due to a lower success rate. A great deal of work and investigation is in progress to improve outcomes, taking into consideration even the newly available immunosuppressive agents and micro-encapsulation techniques. The latter are designed to separate the insulin-producing cells from cell-mediated rejection. However, even if this might become an efficient procedure, similar to whole pancreas transplantation, its feasibility will be heavily dependent on organ availability.

Several alternative sources of insulin-producing cells are currently being examined. This includes the use of tissues from other species (pigs represent the most suitable donor species) and engineered human non-beta cells.

#### Stem Cells

Stem cells and progenitor-based approaches have become the focus of high expectations, as effective generation of beta cells might provide an unlimited source of self-tolerated insulin-producing cells. Stem cells are characterised by self-renewal capacity and the ability to differentiate into various different cell types. This includes embryonic stem (ES) and adult stem (AS) cells. The first successful differentiation of mouse ES cells into pancreatic lineage was attained through transfection of a drug-resistant gene under control of the insulin promoter, followed by cell lineage selection and maturation.

After *in vitro* differentiation, one transgenic ES cell clone showed regulated insulin release and, after transplantation, normalised glycaemia in streptozotocin-induced diabetic mice. Subsequent modifications have been used to generate functional islet-like clusters. However, a feature of undifferentiated ES cells is their tumourigenic potential.

AS cells are involved in the maintenance and regeneration of tissues. Moreover, they may transdifferentiate into various cell types of other lineages with much lower tumourigenic potential. Propagation and direction of multipotent AS cells into the pancreatic lineage *in vitro* would allow a sufficient amount of transplantable cells to be generated. A successful generation of insulin-releasing cells was reported from different pancreatic sources. Using stem cells derived from easily accessible tissues, such as bone marrow, might provide an optimal strategy.

Normalisation of blood glucose levels through cell replacement strategies is obviously the objective of all these procedures. However, until now, there little attention has been paid to other aspects of islet function, including the regulatory roles of glucagon, somatostatin and pancreatic polypeptides in carbohydrate, protein and lipid metabolism. It is also clear that any therapeutic application of stem cells in diabetes therapy is still far away.

### Artificial Pancreas

An alternative approach to beta cell replacement is the artificial pancreas, i.e. a closed-loop portable device with the capacity of continuous measurement of blood glucose concentration and appropriate delivery of insulin for maintenance of normoglycaemia (see *Figure 2*). Although components necessary to assemble an artificial pancreas (insulin pump, glucose sensor and mathematical algorithm of control) are available, further work is needed to ensure co-ordinated interaction between them and persistent reliability of blood glucose reading and insulin delivery.

Major advances have been obtained for each of these components. Thus, 'smart pumps' have been developed. Once supplied with information on

subcutaneous fibre microdialytic or reverse iontophoresis systems, however, are handicapped by substantial lag time between glucose changes in blood and interstitial fluids. The development of systems capable of realtime glucose reading and assessment of glycaemic trends might provide the possibility for a closed-loop insulin delivery system.

### Conclusions

Diabetes has always represented a formidable arena for new and modern advances in therapeutic solutions. Insulin discovery was a landmark in medical research of isolating a hormone for therapeutic use. Recombinant DNA technology has initially been used to synthesise the first 'human' hormone, i.e. insulin. Insulin is the first hormone to be engineered to obtain analogues with well-specified pharmacokinetic and pharmacodynamic properties.

Diabetes research will continue to provide cutting-edge solutions in the attempt to achieve independence from multiple administration of insulin, recovery of physiological insulin sensitivity and secretion. Nonetheless, major research efforts and a substantial

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blood glucose levels and meal carbohydrate content, the microcomputer of the pump, based on the insulin/carbohydrates ratio, the individual insulin sensitivity, glycaemic targets and residual insulin activity of previous bolus will suggest the appropriate insulin dose for the meal. However, for the purpose of closing the loop, using implantable pumps with intraperitoneal insulin delivery appears to be the best approach.

Essential in the development of a miniaturised artificial pancreas is a reliable and long-lasting glucose sensor. Continuous glucose monitoring of glycaemia can be achieved through measurement of glucose concentration in the vascular bed or interstitial fluids or by studying the effects of the glucose on tissues. Intravenous continuous glucose sensing is unlikely to be the solution, particularly in long-term glucose monitoring. The current

amount of time will be required to achieve these ambitious goals. In the meantime, diabetes will continue to pose a great challenge to the patient, the physician and the industry. At present, the greatest challenge is to ensure good glycaemic control and, thus, better chances of reducing the risk and the burden of diabetic complications for as many diabetic patients as possible.

With the course of time new solutions will become available and it is imperative for physicians to use all of these solutions at full capacity. This requires awareness of the importance of strict glycaemic control and the need for an uncompromising 'treat-to-target' approach. ■

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