Future treatment strategies for diabetes

Michael Kirby

Tight glycaemic control was proved essential by the UK Prospective Diabetes Study and the Diabetes Control and Complications Trial. However, current therapies often fail to reach and maintain appropriate targets for glucose control. Clinical and scientific research continues to discover potential therapeutic targets that may lead to improvements in glycaemic management. This review highlights some of the latest advances in diabetes research, concentrating particularly on new technologies and therapies that are likely to enter into clinical practice in the near future.

Advances in diabetes research have led to a reassessment of treatment goals for diabetes. Evidence from the UK Prospective Diabetes Study (UKPDS) in type 2 diabetes and the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes definitively demonstrated the importance of tight glycaemic control in reducing the risk of diabetes complications (UKPDS Group, 1998; DCCT Research Group, 1993). The next 10 years will be defined by the introduction of new therapeutic modalities and by the degree to which these new treatments can help us address the lessons learned from the UKPDS and DCCT.

The need for improved therapies

The DCCT and the UKPDS found that in both type 1 and type 2 diabetes, target levels of HbA_{1c} were extremely difficult to achieve and maintain. The DCCT aimed for HbA_{1c} levels as close to normal as possible (<6.05 %). While 44 % of patients receiving intensive therapy reached this goal at some point during the trial, only 5 % maintained an average value in this range (DCCT Research Group, 1993). Similarly, the target HbA_{1c} level for intensive therapy in the UKPDS was <7.0 %. However, after 6 years of intervention, less than 50 % of patients reached this goal, even with a combination of oral antidiabetic agents and insulin (UKPDS Group, 1995).

Limitations of current therapies for type 2 diabetes

Insulin and five classes of oral therapy (sulphonylureas, meglitinides, biguanides, glitazones and α-glucosidase inhibitors) are currently available to treat diabetes.

Insulin

Although insulin is the most effective therapy for lowering HbA_{1c}, the risk of hypoglycaemia is always present. Furthermore, the need to inject insulin can present psychological barriers for either intensifying insulin therapy in type 1 diabetes or initiating insulin therapy in type 2 diabetes (Zambanini et al, 1999; Polonsky and Jackson, 2004).

Sulphonylureas

Sulphonylureas bind to ATP-dependent potassium channels (K^+_{ATP}), on pancreatic β-cells, causing insulin secretion (Fuhlendorff

Article points

1. Current diabetes therapies have limitations in terms of glycaemic control.
2. The next 10 years will be defined by the introduction of new therapeutic modalities.
3. Strategies will include restoring β-cell function, improving insulin sensitivity, reducing hepatic glucose output and weight reduction.
4. Also, non-invasive insulin delivery should become a reality.
5. It is up to practitioners to prepare themselves for the introduction of these emerging therapies to ensure that these developments translate into maximal patient benefit.

Key words

- Glycaemic control
- Insulin sensitivity
- Weight reduction
- Non-invasive insulin delivery

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Page points

1. Although initially providing good glycaemic control, sulphonylureas become less effective over time as the β-cells of the pancreas progressively fail.
2. Meglitinides only work in patients with remaining β-cell function.
3. While being effective in lowering fasting glucose levels, metformin has a range of contraindications and associated precautions.
4. Troglitazone, the first glitazone to reach the market, was withdrawn because of reports of liver toxicity, while in rosiglitazone and pioglitazone other safety issues are of clinical concern.
5. α-Glucosidase inhibitors are associated with gastrointestinal side effects such as flatulence and diarrhoea.

et al, 1998). However, this oral therapy class has several drawbacks. As with all treatments that raise insulin levels, there is a risk of hypoglycaemia (Ferner and Neal, 1988). Sulphonylureas can also cause significant weight gain (UKPDS Group, 1998). Furthermore, although initially providing good glycaemic control, sulphonylureas become less effective over time as the β-cells of the pancreas progressively fail.

Meglitinides

Meglitinides (repaglinide and nateglinide) have a similar mechanism of action to sulphonylureas, but have a much shorter duration of action and cause a transient increase in insulin secretion (Fuhlendorff et al, 1998). Therefore, they carry lower, but not absent, risks of hypoglycaemia and weight gain (Marbury et al, 1999; Hanefeld et al, 2000; Horton et al, 2000). These agents are useful when post-meal hyperglycaemia is a particular problem. As with sulphonylureas, though, meglitinides only work in patients with remaining β-cell function.

Biguanides

Metformin is the only member of the biguanide family that is licensed for the treatment of type 2 diabetes and it is a first-line therapy. Although the mechanism of action of metformin is not fully defined, it appears that metformin decreases hepatic glucose output (Gunton et al, 2003). While being effective in lowering fasting glucose levels, metformin has a range of contraindications and associated precautions, including renal disease or renal dysfunction, congestive heart failure, age ≥80 years, hepatic disease and presence of hypoxic conditions (such as chronic obstructive pulmonary disorder and acute myocardial infarction). It is also associated with the rare, but often fatal, side effect of metabolic acidosis (Holstein et al, 1999; Lebovitz, 2004).

Glitazones

Glitazones (rosiglitazone and pioglitazone) bind to, and activate, a nuclear hormone-binding receptor known as peroxisome proliferator-activated receptor-gamma (PPARγ; Vasudevan and Balasubramanyam, 2004). The molecular mechanism of action is not yet fully defined, but PPARγ activation regulates the expression of a number of genes involved in the control of glucose and lipid metabolism, leading to an increase in insulin sensitivity of adipose and muscle tissue (Vasudevan and Balasubramanyam, 2004).

Troglitazone was the first member of this class to reach the market, but was withdrawn shortly afterwards because of reports of severe liver toxicity. While rosiglitazone and pioglitazone do not appear to share the liver toxicity of troglitazone, some safety issues, such as the induction of oedema and exacerbation of congestive heart failure, are of clinical concern (Vasudevan and Balasubramanyam, 2004). As with insulin secretagogues, glitazones can induce significant weight gain (Vasudevan and Balasubramanyam, 2004). However, these drugs may confer benefits to cardiovascular risk factors (lipids, blood pressure and microalbuminuria) and are a useful second-line therapy, combined with metformin in the obese patient.

α-Glucosidase inhibitors

Acarbose and voglibose bind to α-glucosidases in the small intestine and slow the breakdown of carbohydrates into glucose and prevent excessive rises in post-meal plasma glucose (Bischoff, 1994). But these agents do not lower HbA_{1c} as much as sulphonylureas or glitazones do and they are associated with gastrointestinal side effects such as flatulence and diarrhoea (Lebovitz, 2004).

Table 1. Single-pill combination therapies for type 2 diabetes.

Trade name	Active ingredients	Defects targeted	Status
Metaglip	Glipizide Metformin	Sulphonylurea (insulin secretagogue) Insulin sensitiser (reduces hepatic glucose output)	Launched in the US and Europe
Avandamet	Rosiglitazone Metformin	Increases whole-body insulin sensitivity Insulin sensitiser (reduces hepatic glucose output)	Launched in the UK in November 2003
Avandaryl	Glimepiride Rosiglitazone	Sulphonylurea (insulin secretagogue) Increases whole-body insulin sensitivity	Pre-registration in the UK
Actoplus Met	Metformin Pioglitazone	Increases whole-body insulin sensitivity Insulin sensitiser (reduces hepatic glucose output)	Pre-registration in the US; EMEA submission awaited
Glucovance	Glyburide Metformin	Sulphonylurea (insulin secretagogue) Insulin sensitiser (reduces hepatic glucose output)	Launched in the US; pre-registration in France under the mutual recognition scheme

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1. Single-pill combination formulations may increase compliance and be cheaper than the prescription of two separate medicines.
2. Pancreas transplantation is an effective therapy for type 1 diabetes, but is restricted to patients with serious, progressive complications.
3. Islet cell transplantation is a less invasive procedure and therefore a safer and less costly option.
4. Natural GLP-1 is rapidly degraded and eliminated from the body, but longer-acting GLP-1 analogues are being developed.

Emerging treatment strategies for diabetes

Several new categories of therapy will be introduced over the coming years. Many single-pill combinations of existing therapies for type 2 diabetes will become available. Moreover, new therapeutic approaches to both type 1 and type 2 diabetes will add to practitioner treatment options.

Single-pill combination therapies for type 2 diabetes

The UKPDS and DCCT highlighted the importance of lowering hyperglycaemia as effectively as possible. This has placed an emphasis on early combination therapy, and many single-pill combination formulations have or will become available (*Table 1*). These formulations may increase compliance and be cheaper than the prescription of two separate medicines, but as they are fixed-dose regimens, some of the capacity to adjust doses on an individual basis is lost.

Restoring physiological β-cell function

In type 1 diabetes, a restoration of β-cell function can only be achieved by a pancreatic or islet cell transplantation. However, a loss of β-cell function is a major, progressive defect in type 2 diabetes that is the focus of intensive research.

Pancreas and islet cell transplantation

Pancreas transplantation is an effective therapy for type 1 diabetes, but is restricted to patients with serious, progressive complications as the concomitant lifelong immunosuppressive therapy required, and the operation itself, is associated with significant morbidity (Robertson et al, 2000). Islet cell transplantation is a less invasive procedure and therefore a safer and less costly option. Immunosuppression is still required with islet cell transplantation and success to date has been limited, although refinements in techniques promise better outcomes in the future (Ryan et al, 2002).

GLP-1 and DPP-IV inhibitors

Glucagon-like peptide-1 (GLP-1) is a peptide hormone that augments insulin secretion in response to elevated blood glucose. It is secreted from the intestinal mucosa in response to a meal and, in addition to its incretin effect, inhibits the secretion of glucagon, reduces gut motility and increases satiety (Holst, 2002).

GLP-1 improved glucose control when administered by subcutaneous injection to

patients with type 2 diabetes (Zander et al, 2002). However, natural GLP-1 is rapidly degraded and eliminated from the body, and longer-acting GLP-1 analogues are being developed.

One such development is the injectable GLP-1 peptide analogue derived from the saliva of the Gila monster lizard. This peptide, called exenatide, dose-dependently reduced HbA_{1c} levels in sulphonylurea-treated patients (Buse et al, 2004) and metformin-treated patients (DeFronzo et al, 2005) when subcutaneously injected twice daily for 30 weeks. In April 2005, the US Food and Drug Administration (FDA) approved exenatide for the adjunctive therapy of type 2 diabetes, and clinical trials of exenatide as monotherapy are ongoing. The companies developing exenatide expect to seek regulatory review in other countries in the future (PRNewswire, 2005a). Other GLP-1 analogues in development are shown in *Table 2*.

Dipetidyl peptidase-IV (DPP-IV) is a cell-surface peptidase that inactivates GLP-1 by cleaving two amino acids from the incretin's amino terminus. The development of small-molecule DPP-IV inhibitors could lead to an orally active therapy to raise GLP-1 activity. Data from a randomised, placebo controlled trial of the DPP-IV inhibitor vildagliptin in patients treated with metformin support these assertions (Ahren et al, 2004).

Importantly, the effects on glucose control observed after 12 weeks were maintained during an extension of the trial to 52 weeks. Furthermore, those randomised to vildagliptin showed little deterioration in glycaemic control, whereas those assigned to placebo experienced the usual pattern of progression towards failure with metformin therapy (Ahren et al, 2004). As with GLP-1 analogues, a number of DPP-IV inhibitors are in clinical development (*Table 2*).

To date, both GLP-1 analogues and DPP-IV inhibitors appear to be generally well tolerated. An increase in mild-to-moderate gastrointestinal adverse events compared with placebo has been reported for GLP-1 analogues (Madsbad et al, 2004; DeFronzo et al, 2005), and in the 52-week DPP-IV inhibitor study, the profile of adverse events was similar in the active and placebo arms (Ahren et al, 2004).

Amylin analogues

Amylin is a 37-amino acid peptide that is co-secreted from the β-cells of the pancreas with insulin. When secreted to excess, it

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Table 2. Examples of GLP-1 analogues and DPP-IV inhibitors in clinical development.

Drug	Company	Mode of action	Status
Byetta (exenatide)	Amylin/Eli Lilly	GLP-1 analogue	Registered in the US; approval sought in other countries
MK-431	Merck & Co	DPP-IV inhibitor	Phase III
Vildagliptin	Novartis	DPP-IV inhibitor	Phase III
AVE-0010	Sanofi-Aventis	GLP-1 analogue	Phase II
CJC-1131	ConjuChem	GLP-1 analogue	Phase II
Liraglutide	Novo Nordisk	GLP-1 analogue	Phase II
PSN-9301	Prosidion	DPP-IV inhibitor	Phase II
Saxagliptin	Bristol-Myers Squibb	DPP-IV inhibitor	Phase II
SUN-E7001	Daiichi Suntory Pharma/Sankyo	Recombinant GLP-1 (nasal delivery formulation)	Phase I
TH-0318	Theratechnologies	Long-acting GLP-1 analogue	Phase I

Table 3. Examples of PPAR agonists currently in clinical development.

Drug	Company	Mode of action	Status
Muraglitazar	Bristol-Myers Squibb	PPARα-γ agonist	Pre-registration in US; scheduled for worldwide commercialisation
Galida (tesaglitazar)	AstraZeneca	PPARα-γ agonist	Phase III
FK614	Fujisawa-Yamanouchi	PPARγ agonist	Phase II
Naveglitazar	Ligand/Eli Lilly	γ-Dominant PPARα-γ agonist	Phase II
Metaglidasen	Metabolex	Partial PPARγ agonist	Phase II
T131	Tularik-Amgen	Selective PPARγ agonist	Phase II
TAK-654	Takeda	PPARα-γ agonist	Phase II

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1. In clinical trials, pre-meal injections of pramlintide have significantly improved glycaemic control in people with type 1 diabetes or insulin-treated type 2 diabetes.
2. Transgenic mice lacking the PTP1B gene display enhanced insulin sensitivity and do not develop diabetes or gain weight when provided with a high-calorie diet.
3. The aim for next-generation PPARs is better antidiabetic activity with better tolerability.
4. New PPARs that target both α and γ forms of the receptor are in development.

forms insoluble islet amyloid deposits that can lead to β-cell destruction (Porte and Khan, 1989), but it also plays a role in glucose metabolism. Amylin acts as a neuroendocrine hormone and binds to specific receptors in the brain, causing a suppression of glucagon secretion and slowing gastric emptying (Weyer et al, 2001). These effects work with those of insulin to prevent post-meal hyperglycaemia (Weyer et al, 2001).

Symlin (pramlintide) is a soluble peptide analogue of amylin. In clinical trials, pre-meal injections of pramlintide have significantly improved glycaemic control in people with type 1 diabetes or insulin-treated type 2 diabetes (Whitehouse et al, 2002; Hollander et al, 2003). HbA_{1c} levels were reduced by approximately 0.7% in people with type 1 or type 2 diabetes after 2–3 weeks of therapy. Furthermore, pramlintide therapy was associated with weight loss in both sets of individuals. In March 2005, pramlintide was approved by the FDA for use in combination with insulin and the developers are in ongoing discussions with the European Medicines Agency (EMEA) for approval throughout the EU.

Improving insulin sensitivity

The discovery that glitazones worked through the activation of PPARγ has prompted much effort in the development of more potent PPARs with fewer adverse events. In addition, research into the biochemical pathways that are altered in insulin-resistant states has uncovered new therapeutic targets. Protein tyrosine phosphatase 1B (PTP1B) is one such target.

PTP1B inhibitors

PTP1B is a member of a class of cell-signalling enzymes involved in the regulation of many cellular processes. Transgenic mice lacking the PTP1B gene display enhanced insulin sensitivity and do not develop diabetes or gain weight when provided with a high-calorie diet (Klaman et al, 2000). The search is now on to see if PTP1B inhibitors can mimic these effects in humans, and there are at least 12 candidates in preclinical development.

Next-generation PPARs

The aim for next-generation PPARs is better antidiabetic activity with better tolerability. Agents such as metaglidasen act as 'selective' PPARγ agonists, which maintain the antidiabetic activity, but may have fewer side effects (Metabolex, 2005).

It has been well established that PPARα agonists, such as the fibrates, can raise high-density lipoprotein cholesterol levels. New PPARs that target both α and γ forms of the receptor are in development. These have the potential to improve glycaemic control and

the dyslipidaemia that is characteristic of type 2 diabetes. *Table 3* summarises some of the PPAR agonists currently in development for the treatment of type 2 diabetes.

Reducing hepatic glucose output

In individuals with good insulin sensitivity of the liver, insulin switches off hepatic glucose output in the fed state. Hepatic glucose output is a major determinant of fasting glucose levels and is increased in type 2 diabetes. Glycogen phosphorylase catalyses the breakdown of glycogen to glucose in the liver (Oikonomakos, 2002) and one glycogen phosphorylase inhibitor, AVE-5688, is in phase I clinical trials for the treatment of diabetes.

Another target is glycogen synthase kinase-3 (GSK-3), which is a major determinant of glycogen formation. GSK-3 phosphorylates and inactivates glycogen synthase and a number of GSK-3 inhibitor candidates are in preclinical development (Meijer et al, 2004). Finally, as glucagon opposes the actions of insulin and increases hepatic glucose output, many companies are in the early stages of developing liver-specific glucagon receptor antagonists for the treatment of diabetes (Dallas-Yang et al, 2004).

Treatment through weight reduction

The connection between excess body weight and type 2 diabetes presents a strong rationale for the use of weight-reducing agents to treat or prevent this disease. Xenical (orlistat) is a lipase inhibitor that blocks the absorption of about 30 % of dietary fat from the gastrointestinal tract.

A randomised trial has shown that orlistat can reduce the risk of diabetes in overweight and obese individuals by 37 % compared with placebo (P=0.0032; Torgerson et al, 2004). Furthermore, orlistat was associated with significant improvements in glycaemic control in a randomised, placebo-controlled trial in people with metformin-treated type 2 diabetes (Berne and the Orlistat Swedish Type 2 diabetes Study Group, 2005). In this trial, 52 weeks of orlistat therapy produced significant weight loss compared with placebo (–5.0 % versus –1.8 %; P<0.0001) and concomitant improvements in HbA_{1c} (–1.1% versus –0.2%; P<0.0001; Berne and the Orlistat Swedish Type 2 diabetes Study Group, 2005).

The adverse events associated with orlistat include oily or liquid stools, oily spotting and faecal urgency, but these can be minimised by sticking to a low-fat diet.

In the majority of cases, it is not losing weight that is the biggest problem, but maintaining that weight loss in the long term. A new drug called rimonabant may provide a solution. This agent, which is in phase III trials for the treatment of obesity,

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Table 4. Current status of some pulmonary insulin delivery devices.

Product/device	Company	Type of insulin used	Status
Exubera	Nektar Therapeutics/ Pfizer/Sanofi-Aventis	Dry powder	Under review by FDA and EMEA
Aerodose inhaler	Aerogen	Liquid	Phase II
AERx insulin Diabetes Management System	Aradigm/Novo Nordisk	Liquid	Phase II
AIR pulmonary drug delivery system	Alkermes/Eli Lilly	Human insulin inhalation powder	Phase II

Note: many other pulmonary insulin products and devices are in phase I clinical trials.

blocks cannabinoid receptors in the central nervous system and depresses appetite (Vickers and Kennett, 2005). Interestingly, rimonabant is also being investigated for smoking cessation and other drug dependencies (Le Foll and Goldberg, 2005).

The Rimonabant in Obesity – Europe trial randomised 1507 patients with a body mass index ≥27 kg/m2 and additional cardiovascular risk factors to receive rimonabant or placebo for 2 years. Compared with placebo, completers on rimonabant lost a mean of 4.7 kg over the 2 years of the study (P<0.001; Van Gaal, 2005). It remains to be seen, though, if this weight loss is maintained over longer time periods.

Advances in insulin therapy: The era of non-invasive insulin delivery

Perhaps the most exciting advance in insulin therapy is that of non-invasive insulin delivery systems. An intra-nasal formulation of insulin is in phase II clinical trials in Ireland (Bentley Pharmaceuticals, 2005), while the quest for transdermal and oral insulin formulations continues. Pulmonary delivery systems, however, are the most advanced non-invasive strategies in development (*Table 4*; Cefalu, 2004).

One form of inhaled insulin (Exubera) has been accepted for full review by the FDA and is under review by the EMEA (PRNewswire, 2005b). This system uses a dry-powder formulation of rapid-acting human recombinant insulin that is inhaled orally via a simple, re-usable inhaler (Cefalu, 2004). Such systems can reduce the number of injections needed to maintain tight glycaemic control and may encourage the earlier initiation of insulin therapy in type 2 diabetes patients – an objective that is supported by a growing body of diabetes experts (Wallace and Matthews, 2000; Campbell and White, 2002; Home et al, 2003).

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2. Perhaps the most exciting advance in insulin therapy is that of non-invasive insulin delivery systems.
3. Such systems can reduce the number of injections needed to maintain tight glycaemic control and may encourage the earlier initiation of insulin therapy in type 2 diabetes patients.
4. Pulmonary delivery systems are the most advanced non-invasive strategies in development.
5. One form of inhaled insulin (Exubera) has been accepted for full review by the FDA and is under review by the EMEA.

Conclusions

Recent advances have brought the aim of tight glycaemic control ever closer, but present day therapies fall short of ideal. However, the future of antidiabetic therapy looks bright, with many novel therapies in late-stage development. These new treatments are spread across a range of therapeutic targets and raise the possibility of simultaneously addressing the multiple defects that underlie the onset and progression of type 1 and type 2 diabetes. It is up to practitioners to prepare themselves for the introduction of these emerging therapies to ensure that these developments translate into maximal patient benefit.

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'Recent advances have brought the aim of tight glycaemic control ever closer, but present day therapies fall short of ideal. However, the future of antidiabetic therapy looks bright, with many novel therapies in late-stage development.'

'It is up to practitioners to prepare themselves for the introduction of these emerging technologies to ensure that these developments translate into maximal patient benefit.'