

New frontiers in the management of type 2 diabetes

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Type 2 diabetes is a chronic, debilitating disease characterized by insulin resistance, impaired insulin secretion, and hyperglycaemia, and afflicting at least 171 million people worldwide (31.7 million in India). This chronic disease is not benign and patients with diabetes suffer from numerous microvascular and macrovascular complications which cause a lot of morbidity and mortality. Results from the UKPDS (United Kingdom Prospective Diabetes Study) clearly demonstrate that tight glucose and blood pressure control in patients with type 2 diabetes prevents the development of and delays the progression of microvascular complications and possibly macrovascular disease. In addition, results from the UKPDS and other studies like the Heart Protection Study (HPS) have also shown that treatment of concomitant risk factors like lipids and blood pressure and the use of aspirin have favourable effects on cardiovascular complications and mortality in patients with type 2 diabetes. In order to achieve glycaemic goals, we have several anti-hyperglycaemic agents in our therapeutic armamentarium today. However, despite their availability, we have not been able to achieve glycaemic goals in our patients with diabetes due to a variety of reasons. However, there appears to be hope for the future. The progress of research in all fields of diabetes therapeutics from diabetes treatment to continuous glucose monitoring systems to novel insulin delivery systems has been spectacular. These advances have resulted in newer pharmacologic agents, implantable glucose sensors and inhaled insulin. There is also hope that large scale implementation of intensive lifestyle programmes and education efforts may help to prevent diabetes in high risk individuals. Indeed, the repertoire of options and strategies currently available (and in the pipeline) to treat and prevent/delay diabetes and its complications is impressive. In this review, we will discuss the evolving cardiovascular benefits of the thiazolidinediones (TZDs); describe in detail the newer glucose lowering gut hormones with novel mechanisms of action; delineate the recent advances in non invasive insulin delivery systems (including inhaled insulin); review the ongoing developments in continuous glucose measuring devices and finally present an update on the prevention of diabetes.

Key words Glucose lowering agents - non invasive insulin therapy - recent advances - treatment - type 2 diabetes

Type 2 diabetes is a chronic, debilitating disease characterized by insulin resistance, impaired insulin secretion, and hyperglycaemia and afflicting at least 171 million people worldwide (31.7 million in India). Even more concerning is the fact that this figure is likely to more than double to 366 million (79.4 million in India) by 2030¹. This chronic disease is not benign and patients with diabetes suffer from numerous microvascular and macrovascular complications which cause a lot of morbidity and mortality. The microvascular complications include diabetic retinopathy, nephropathy and neuropathy which lead to significant morbidity in the form of preventable blindness, end-stage renal disease and limb amputations. In the USA, diabetes is the leading cause of blindness, end-stage kidney disease and non-traumatic amputations². In addition to microvascular complications, diabetics also suffer from macrovascular complications in the form of accelerated atherosclerosis and premature cardiovascular disease (CVD). A pathophysiologic hallmark of type 2 diabetes is insulin resistance, which has both genetic and acquired components³. Glucose intolerance and hyperglycaemia supervene only when the pancreatic beta cells are unable to maintain compensatory hyperinsulinaemia to overcome tissue resistance to insulin action⁴. However, in addition to having hyperglycaemia and insulin resistance/secretory defects, nearly 80 per cent of diabetics are obese and have a host of other metabolic abnormalities, including dyslipidaemia [increased small dense, low density lipoprotein (LDL) cholesterol, decreased high density lipoprotein (HDL) cholesterol, and raised triglyceride levels], hypertension, and abnormalities of coagulation and the fibrinolytic system. This cluster of metabolic abnormalities, which has been termed the metabolic syndrome⁵ or the cardiovascular dysmetabolic syndrome⁶ is associated with a higher incidence of premature cardiovascular morbidity and mortality.

The treatment targets for patients with type 2 diabetes include a glycaemic goal of <6.5 per cent⁷ or <7 per cent⁸; pre-prandial capillary plasma glucose 90-130 mg/dl; peak post-prandial plasma glucose

<180 mg/dl; LDL <100 mg/dl (<70 mg/dl in the presence of diagnosed CVD); triglycerides <150 mg/dl; HDL >40 mg/dl (>50 mg/dl in women) and blood pressure <130/80 mmHg (<125/75 with proteinuria)⁸. In order to achieve the above glycaemic goals, we have several anti-hyperglycaemic agents in our therapeutic armamentarium today, including the insulin secretagogues - sulphonylureas and meglitinides (nateglinide and repaglinide); alpha-glucosidase inhibitors (acarbose and miglitol); biguanides (metformin); thiazolidinediones - TZDs (rosiglitazone and pioglitazone); the rapid acting insulin analogues (aspart, lispro, glulisine); and the long acting non-peaking insulin analogues (glargine and detemir)^{9,10}.

Despite the availability of all the above medications and also numerous glucose measurement devices, we have not been able to achieve glycaemic and other goals in our patients with diabetes. In a recent study from the USA¹¹, only 37 per cent of individuals achieved a glycosylated haemoglobin A1c (HbA1c) level less than the American Diabetes Association (ADA) goal of 7 per cent. Even more disappointing was the fact that overall only 7.3 per cent of individuals in this cohort achieved optimal glycaemic, lipid and blood pressure targets. Limited data are available from other countries, but it is unlikely that the numbers will be any more encouraging. Sub-optimal glucose, lipid and hypertension control play a major role in the mortality burden of nearly 3.2 million deaths annually due to diabetes⁷. Globally, one in 20 deaths is attributable to diabetes and as a result of this disease, there are 8,700 deaths every day, *i.e.*, six deaths every minute⁷. However, the development of diabetic complications and premature cardiovascular mortality is no longer inevitable. Results from the UKPDS (United Kingdom Prospective Diabetes Study) clearly demonstrate that tight glucose and blood pressure control in patients with type 2 diabetes prevents the development of and delays the progression of microvascular complications and possibly macrovascular disease^{12,13}. In addition, results from the UKPDS and other studies like the

Heart Protection Study (HPS) have also shown that treatment of concomitant risk factors like lipids and blood pressure and the use of aspirin have favourable effects on cardiovascular complications and mortality in patients with type 2 diabetes¹⁴⁻¹⁶.

However, we are still not able to achieve glycaemic and non glycaemic goals in patients with diabetes due to a variety of reasons. Clearly, economic factors and limited access to physicians who are knowledgeable in diabetes management are important barriers to achieving ideal glucose control in our patients. Patient compliance is also an important issue. But it is important to recognize that other factors may also play a role. These include the undesirable side effects and limitations of the currently available oral anti-hyperglycaemic agents, the limitations of the current insulin delivery devices and the drawbacks of the present glucose measurement devices. However, there appears to be hope for the future with the emergence of evolving data on the cardiovascular benefits of the TZDs, the approval of two new gut hormone analogues with novel mechanisms of action (exenatide and pramlintide), the ongoing progress in alternative modes of insulin delivery (including the recent approval of inhaled insulin) and the development of newer and more reliable continuous glucose measurement devices (both external and implantable). Finally, with the recent publication of the results from the Diabetes Prevention Program¹⁷ and other studies, the prospect of preventing type 2 diabetes in high risk individuals is an exciting and attainable prospect.

In this review, we will discuss the evolving cardiovascular benefits of the TZDs; describe in detail the newer glucose lowering gut hormones with novel mechanisms of action; delineate the recent advances in non invasive insulin delivery systems (including inhaled insulin); review the ongoing developments in continuous glucose measuring devices and finally present an update on the prevention of diabetes. Not discussed in this article are developments in islet cell transplantation which

is still at an early though encouraging stage with the availability of new less toxic immunosuppressive agents.

Evolving cardiovascular benefits of the thiazolidinediones

Type 2 diabetes is associated with a 2-4 fold increased risk of cardiovascular events that carry a poor prognosis¹⁸. The risk of cardiovascular complications in patients with diabetes is equivalent to that of people without diabetes who have suffered previous acute myocardial infarction¹⁹. Further, people with diabetes have not benefited to the same degree as those without diabetes in terms of recent reductions in cardiovascular mortality and there is an overall 25 per cent reduction in life expectancy compared with the general population (mainly due to cardiovascular deaths)²⁰. Due to their glucose-lowering properties, anti-hyperglycaemic agents significantly reduce the risk of the microvascular complications in patients with diabetes^{13,14}. However, no glucose-lowering agent has clearly been shown to significantly reduce macrovascular cardiovascular disease. Even in the UKPDS, although metformin monotherapy was associated with a significant decrease in CVD mortality, the addition of metformin to sulphonylurea therapy was associated in a significant 96 per cent increased risk of diabetes-related death¹³.

The TZDs - rosiglitazone and pioglitazone, were introduced in the late 1990s and constitute a class of oral antidiabetic agents which are “insulin sensitizers” since they exert direct effects on the mechanisms of insulin resistance²¹. Through their peroxisome proliferator-activated receptor (PPAR) γ agonist effects, the TZDs not only improve insulin sensitivity and glycaemic control with reduced insulin requirements, but also have potentially favourable effects on other components of the metabolic syndrome²¹. These beneficial effects on lipid metabolism, blood pressure, vascular tone and endothelial function might directly and indirectly influence cardiovascular risk by favourably altering

several pro-atherogenic metabolic processes and slowing the progression of premature CVD. Several studies to date have shown that TZD treatment not only reduces the progression of carotid IMT (intimal medial thickening) but also the proliferation of neointimal tissue after coronary stent implantation in diabetic patients²². However, until recently there have been no data on hard CVD outcomes in diabetic patients using TZDs.

The PROspective pioglitAzone Clinical Trial In macroVascular Events Study (PROactive Study) was a prospective, randomized, controlled trial in 5238 patients with type 2 diabetes who had evidence of pre-existing cardiovascular disease²³. These patients were randomized to pioglitazone 45 mg daily, or placebo in addition to the patient's usual glucose lowering medications. Investigators were required to treat all patients to optimal glucose, lipid and blood pressure goals. Thus this study was designed to assess the effect of pioglitazone on CVD, independent of its glucose lowering effects. After an average follow up of about 3 yr, the results of the study showed that pioglitazone had a modest, but not statistically significant, 10 per cent reduction in the risk of the primary composite endpoint, which consisted of all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndrome, and revascularization or amputation. However, the "main secondary endpoint," consisting of certain of the primary outcome measures, namely all-cause mortality, myocardial infarction, and stroke, was significantly reduced by 16 per cent. Of note, in this study was that pioglitazone treatment was associated with an increase in incident congestive heart failure (CHF) in patients. Despite the fact that individuals with New York Heart Association Class II heart failure, or higher, were excluded from study, heart failure both requiring and not requiring hospitalization was significantly increased in the pioglitazone group (10.8% for pioglitazone vs. 7.5% for placebo). However in this study, the criteria for heart failure were not clearly defined and it is unclear whether the frequency of this diagnosis was confounded by

an increased presence of peripheral oedema in the pioglitazone group. On the other hand, it is reassuring that mortality from heart failure was not increased. Also of note, liver function tests actually improved during the duration of the trial.

Although the PROActive study results clearly demonstrated a reduction in all-cause mortality, myocardial infarction, and stroke with pioglitazone, the study was not designed to determine the possible mechanism(s) for this benefit. It is possible that this may be a result of several factors, including the lower HbA1c of 0.5 per cent (probably too small to be the only explanation), a small but significant reduction in blood pressure, as well as changes in the lipid profile, particularly an increase in high-density lipoprotein cholesterol and a lowering of triglycerides²⁴. Given the multiple beneficial effects of the TZDs on improving insulin sensitivity and on traditional and non traditional risk factors, it is tempting to speculate that these anti-atherogenic effects contributed to the results. However, these factors were not assessed in this trial. Also unanswered at present are questions related to whether the PROActive study results observed in Caucasian subjects apply to other ethnic groups and whether treatment with pioglitazone will reduce vascular events in the setting of optimal blood pressure, lipid and glucose control, *i.e.*, whether pioglitazone or other TZDs reduce CVD or non CVD mortality *per se*²⁵. For this, we need to wait for results from other ongoing studies including the action to control cardiovascular risk in diabetes (ACCORD) study - a 7 yr, 10,000 patient study funded by the National Institutes of Health in the USA and designed to evaluate the effects of tight blood pressure, lipid and glucose control (using insulin sensitizers, insulin secretagogues and insulin), on cardiovascular events in patients with type 2 diabetes²⁶; and the Rosiglitazone Evaluated for Cardia Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study - a 6 yr study designed to evaluate whether rosiglitazone, in combination with metformin or sulphonylurea, affects CVD outcomes and progression of diabetes in the long term²⁷.

Recently, there has been an increased interest in the development of dual PPAR γ and PPAR α agonists for the treatment of type 2 diabetes²¹. While the PPAR γ agonists increase insulin sensitivity (thereby explaining the antidiabetic action of the thiazolidinediones rosiglitazone and pioglitazone), the PPAR α agonists, including the fibrates, increase fatty acid oxidation and lead to a decrease in plasma triglycerides and a modest increase in HDL cholesterol. It is expected that agents that activate both PPAR α and PPAR γ would improve glycaemic control similar to the TZDs and also have more beneficial effects on the lipid profile than the TZDs. Muraglitazar is the first dual-PPAR agonist to be considered for general marketing both as monotherapy and combined therapy by the US Food and Drug Administration (FDA). Recent information provided to the FDA revealed that although muraglitazar improved glycaemic and lipid parameters in short-term studies, there was also a 2 to 4 kg increase in weight, a 10 per cent incidence of oedema, and an excess incidence of the composite end point of death, major adverse cardiovascular events myocardial infarction (MI), stroke, transient ischaemic attack (TIA), and congestive heart failure (CHF) in the muraglitazar group compared with placebo or pioglitazone²⁸. The FDA issued an "approvable letter" for this drug and the company, Bristol-Myers Squibb is continuing discussions with the FDA regarding the conduct of additional studies with CVD endpoints or possibly even terminating further development of muraglitazar.

Newer glucose lowering agents

Current therapies for type 2 diabetes are often associated with inadequate control of postprandial hyperglycaemia (especially with the sulphonylureas, metformin and TZDs), weight gain (sulphonylureas, meglitinides, TZDs and insulin), and loss of efficacy over time (a problem with all the current oral agents). A better understanding of physiological responses to meals has led to the development of new agents whose therapeutic action is based on the enhancement of gastrointestinal (GI) hormone action. These agents

might help ameliorate some of the problems mentioned above.

Incretins such as glucagon-like peptide-1 (GLP-1) are naturally occurring hormones released from the GI tract in response to the ingestion of food. GLP-1 is released from the L-cells located in the distal ileum and colon, in response to food containing carbohydrates and fats²⁹. The pleiotropic effects of GLP-1 include enhancement of glucose-dependent insulin secretion from the pancreas, suppression of inappropriately elevated glucagon secretion, delaying gastric emptying, reducing appetite, preserving β -cell function, and increasing β -cell mass (in animal models)³⁰. Importantly, GLP-1 does not suppress normal counter-regulatory increase in glucagon secretion during hypoglycaemia. It is now well known that meal-stimulated circulating levels of GLP-1 are reduced in type 2 diabetes. Thus GLP-1 would seem an appropriate therapeutic agent in patients with type 2 diabetes. However, GLP-1 only has a plasma half-life of approximately 2 min before being degraded by dipeptidyl peptase IV (DPP IV); therefore, its utility as a pharmacologic agent is limited. Exenatide is a synthetic GLP-1 analogue which has a longer half-life because it is not recognized by DPP-IV, thus making it suitable for clinical use³¹.

Exenatide (Byetta®): Exenatide is a 39-amino acid peptide incretin mimetic so named because it mimics the action of GLP-1. It is the synthetic version of exendin-4, an incretin mimetic isolated from the saliva of the Gila monster lizard³². Approximately 53 per cent of the 39-amino acid sequence of GLP-1 is similar to exenatide. Exenatide is the first agent in the class known as incretin mimetics that has been approved for use in the USA as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes who have not achieved adequate glycaemic control with either sulphonylurea or metformin monotherapy or with a sulphonylurea+metformin combination therapy³²⁻³⁵. Its actions result in a slowing of gastric emptying, stimulation of insulin secretion, inhibition of glucagon secretion, improved control of

postprandial hyperglycaemia, and control of body weight. In three recent 30 wk double, blind, placebo controlled studies³³⁻³⁵, in over 1400 patients with a mean HbA1c of approximately 8.5 per cent and mean body weight of about 99 kg, the addition of exenatide 5 µg and 10 µg SQ b.i.d. (to either sulphonylurea or metformin monotherapy or sulphonylurea + metformin combination therapy) resulted in a reduction of HbA1c by 0.6 and 0.9 per cent and body weight by 3.1 and 4.2 kg respectively as compared to placebo. Long-term extension data in 265 patients reveal that the decrease in HbA1c is maintained at week 82 (-1.1% from baseline) and the weight progressively continues to decrease over time (-4.5 kg from baseline). In addition, there were beneficial effects on the lipid profile with small but significant reductions in LDL and triglycerides and an increase in HDL cholesterol. The most commonly reported side effects with exenatide therapy are GI complaints, most commonly nausea. The incidence of nausea is dose-dependent and was consistently seen among patients in the three clinical trials. Nausea occurred most frequently during weeks 0-8 and was generally mild-moderate in nature. Severe nausea ranged from 2.7-6 per cent and withdrawal from the study due to nausea ranged from 1.8-4 per cent. The combination of metformin and exenatide did not result in an increased incidence of nausea. Of note, the weight loss seen with exenatide treatment was not attributable to nausea. Mild to moderate hypoglycaemia occurred more frequently in the exenatide treatment groups when a sulphonylurea was included in the treatment regimen. However, in the exenatide + metformin study, the incidence was the same as the placebo group. Approximately 45 per cent of the patients receiving exenatide were positive for anti-exenatide antibodies, with the majority of titres being in the low range (< 1/125). The presence of these titres did not appear to have a predictive effect on glycaemic response or adverse events.

Exenatide should not be used in patients with type 1 diabetes, those with severe GI diseases, including gastroparesis and in patients with severe renal

impairment. The concurrent use of exenatide with insulin, TZDs, alpha-glucosidase inhibitors, and meglitinides has not been studied. The initial dose of exenatide is 5 µg SQ twice daily administered within 60 min before the morning and evening meals. Exenatide should not be administered after a meal. After 1 month, the dose may be increased to 10 µg SQ twice daily.

An exciting prospect in exenatide therapy is the development of a long acting preparation of exenatide which can be given once a week. In a recent 16 week study, two doses of exenatide LAR given once weekly were not only well tolerated, but also achieved dose-dependent improvements in HbA1c and weight³⁶. Whether these beneficial effects of exenatide are maintained in the longer term and more importantly, whether it has effects on pancreatic β-cell regeneration in humans remain to be determined.

Other GLP-1 analogues: Liraglutide (NN2211) is an acylated human GLP-1 analogue which binds non-covalently to albumin. Since it exhibits a more prolonged pharmacokinetic profile relative to native GLP-1 or exenatide, this drug can be administered once daily. Similar to exenatide, nausea is the most common adverse effect associated with liraglutide administration. In a recent 12 wk trial in 193 patients with type 2 diabetes, 0.75 mg liraglutide SQ daily caused equivalent placebo-adjusted reductions of HbA1c compared with glimepiride (0.75 and 0.74%) from mean baseline values of 7.4-7.9 per cent. In addition, liraglutide treatment was associated with a placebo-adjusted weight reduction of 0.39 kg, whereas patients treated with glimepiride experienced a mean weight gain of 0.94 kg³⁷. In another study, once-daily liraglutide (0.45, 0.6 and 0.75 mg SQ) improved glycaemic control and weight, in a comparable degree to metformin³⁸.

Other albumin-based GLP-1 agonists under investigation include CJC-1131, a DPP-IV-resistant GLP-1 analogue modified with a reactive chemical link that forms a covalent bond with a single amino acid residue within human serum albumin, and

Albugon, a recombinant albumin/GLP-1 hybrid protein³⁹. The ability to link a GLP-1 peptide domain conferring GLP-1R activation to albumin or other proteins that exhibit a more prolonged circulating half life should enable the development of longer-acting GLP-1R agonists suitable for once daily or even weekly administration³⁹.

DPP-IV inhibitors: Orally administered DPP-IV inhibitors are currently in development as glucose lowering agents. Of these, vildagliptin (LAF 237 - Novartis) and sitagliptin (Merck) are in late stages of clinical development.

Vildagliptin: In a recent study, vildagliptin at a dosage of 50 mg/day was compared with placebo for 12 wk (with a further 40 wk extension) in 107 patients with type 2 diabetes on metformin therapy⁴⁰. The placebo-adjusted reduction of Hb A1c from the mean baseline values of 7.7 per cent was 0.6 per cent. At 1 yr, compared to the placebo, vildagliptin (50 mg) reduced the prandial glucose by 43 mg/dl, fasting glucose by 20 mg/dl, fasting insulin levels by 40 pmol/l and HbA1c by 1.1 per cent. In this study, in contrast to exenatide, no significant between-treatment differences in change of weight occurred. mathematical modeling studies have suggested that vildagliptin treatment might improve β -cell function⁴¹.

Sitagliptin (MK-0431-Januvia®): Sitagliptin is the other oral DPP-IV inhibitor in late clinical development. In human studies, sitagliptin once a day increases the postprandial rise in active GLP-1 concentrations without causing hypoglycaemia in normoglycaemic healthy male volunteers⁴². Sitagliptin was recently approved for use in the US as monotherapy and in combination with metformin or a TZD.

Pramlintide (Symmlin®): The mechanism of action of pramlintide does not involve GLP-1 like exenatide and the DPP-IV inhibitors. Pramlintide is an analogue of another gut hormone - Amylin, which is a 37-amino acid peptide co-secreted along with insulin from pancreatic β -cells⁴³. In the pancreatic β cells,

amylin is processed by prohormone convertase, the same enzyme that processes insulin, and is packaged with insulin into the same secretory granules. Both β -cell peptides have similar diurnal patterns, with low fasting levels and robust increases in response to meals⁴⁴. However, amylin circulates at lower plasma levels than insulin (molar ratio of ~1 : 20). Amylin is virtually absent in patients with type 1 diabetes and it is insufficient at mealtime in insulin-requiring patients with type 2 diabetes. However, native amylin is not a suitable therapeutic agent because of its poor solubility and its tendency to aggregate. Hence, an amylin analogue, pramlintide has been developed as a potential pharmaceutical agent with important glucoregulatory actions in humans. Pramlintide slows gastric emptying and suppresses glucagon secretion during the prandial/postprandial period in order to slow and reduce the entry of glucose into the circulation⁴⁴. These actions, in conjunction with those of insulin, help reduce fluctuations in circulating glucose levels to a greater degree than is possible with insulin treatment alone. In clinical studies, pramlintide treatment as an adjunct to insulin decreased HbA1c levels between 0.39 to 0.62 per cent and body weight by 0.5 to 1.4 kg^{45,46}. The combined improvement of glycaemic and weight control makes pramlintide, as an adjunct to insulin therapy, a potentially useful treatment option in overweight and obese patients with type 2 diabetes.

Pramlintide is currently approved for use in the USA as adjunctive treatment to mealtime insulin therapy in patients with type 1 and type 2 diabetes who have been unable to achieve desired glucose control despite optimal insulin therapy (with or without concurrent sulphonylurea or metformin therapy for type 2 diabetes). Because of the effects of pramlintide on gastric emptying, the drug is contraindicated in patients with gastroparesis and also it should not be used in patients taking drugs that alter GI motility or who use the α -glucosidase inhibitors (acarbose, miglitol). The most common side effects with pramlintide therapy is mild to moderate nausea which appears to be dose-related and decreases over time.

Pramlintide has been associated with an increased risk of insulin-induced severe hypoglycaemia, particularly in patients with type 1 diabetes within 3 h following a pramlintide injection. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk. The initial dose is 60 µg given SQ immediately prior to major meals (> 250 kcal or containing >30 g of carbohydrate). The dose of pre-prandial rapid-acting or short-acting insulin (including premixed 70/30 or 75/25 preparations) is reduced by 50 per cent and it is recommended that blood glucose be monitored more frequently. If no clinically significant nausea has occurred for 3-7 days, the dose is increased to 120 µg SQ prior to major meals. (if the 120 µg dose is not tolerated due to nausea, a reduced dose of 60 µg may be used). Once a stable dose of pramlintide has been reached and nausea has subsided, the dose of insulin may be adjusted to optimize glycaemic control.

The use of the above pharmacologic agents which augment the effects of gut hormones is clearly associated with improved glucose control and in the case of exenatide, liraglutide and pramlintide with the added benefit of weight loss. However, at the present time, it is unclear as to what extent the various effects of these agents are mediated through central effects on the brain or peripheral effects in the GI system and also whether these beneficial effects are sustained over the long term²⁹. It is possible that the use of injectable peptides (exenatide, liraglutide and pramlintide) is associated with immunogenicity and the development of neutralizing antibodies that diminish their efficacy over time in some patients. It also remains to be determined whether the use of some of these agents (exenatide, liraglutide, and vildagliptin) will protect β-cells and promote their regeneration as seen in animal studies. On the other hand, recent reports of hyperinsulinaemic hypoglycaemia and nesidioblastosis associated with increased circulating levels of GLP-1 in some patients after gastric bypass surgery highlight the

possible, unwanted long-term consequences of prolonged activation of the GLP-1 receptor in humans²⁹. Long-term studies are needed to answer the above questions and determine the future role of these agents in the treatment of type 2 diabetes.

Alternative non-invasive insulin delivery systems

Inhaled insulin: In type 2 diabetes, the traditional treatment pathway usually involves the initiation of oral hypoglycaemic agent therapy and gradual progression to oral combination agent therapy if diet and lifestyle interventions are not effective⁴⁷. However, once insulin secretory capacity becomes insufficient, many patients do not achieve good glycaemic control with oral agent therapy and require insulin therapy to achieve glycaemic goals and reduce the risk for diabetic complications. This usually involves the addition of basal insulin therapy to oral agents¹⁰. For various reasons, many patients and physicians are often reluctant to initiate subcutaneous insulin therapy⁴⁸. Patients often have a fear of needles and may also object to injection therapy as being inconvenient and unacceptable⁴⁹. Consequently, the pulmonary route has been investigated as an alternative, less invasive method of insulin administration. Inhaled insulin has a faster onset of action than both insulin lispro and regular insulin, and its duration of action is longer than insulin lispro and similar to regular insulin⁵⁰. These characteristics make inhaled insulin suitable for administration before meals to control postprandial glycaemia.

Several studies have shown that in patients with type 1 and type 2 diabetes, inhaled insulin produces glycaemic control similar to that of regular subcutaneous regimens^{51,52}. In addition, the addition of pre-meal inhaled insulin significantly improves glycaemic control in patients with type 2 diabetes who have failed oral agent therapy. In a recent study, inhaled insulin improved overall glycaemic control and HbA1c levels when added to or substituted for dual oral agent therapy with an insulin secretagogue and sensitizer⁴⁷. However, as with other insulin

therapies, there was more hypoglycaemia and mild weight gain with inhaled insulin. Of note, pulmonary function showed no between-group differences in this study.

Exubera® inhaled insulin: The most widely studied insulin product for pulmonary delivery is Exubera (Pfizer), a rapid-acting insulin in powder form. The FDA recently approved Exubera for use in both type 1 and type 2 diabetics⁵³. This particular product contains insulin powder (particle size of $<7.5 \mu\text{m}$) which is packed into blisters with different dosages (1 mg blister = 3 units of insulin and 3 mg blister = 9 units of insulin), and a specialized inhaler is used to deliver the drug to the lungs. The bioavailability of Exubera is approximately 10 per cent when compared with regular human insulin administered by subcutaneous injection⁵⁴. In type 1 diabetes, Exubera inhaled insulin may be used as a replacement for short-acting insulin taken with meals in addition to a basal insulin (NPH/glargine). In type 2 diabetes, Exubera may be used alone or in combination with oral anti-hyperglycaemic agents or longer acting insulin (NPH/glargine). Exubera should not to be used in smokers or in those who recently quit smoking (within the last 6 months). Also, Exubera is not recommended in patients with asthma, bronchitis, or emphysema⁵³. In clinical trials of patients with type 1 or 2 diabetes who were treated with Exubera, the only significant clinical adverse effect was cough. This was generally characterized as mild to moderate in severity, decreased over time and was not associated with declines in lung function. Baseline tests for lung function are recommended after the first 6 months of treatment and every year thereafter, even if there are no pulmonary symptoms⁵⁵.

AERx insulin diabetes management system: In contrast to other delivery systems for inhaled insulin which use powdered insulin, the AERx insulin diabetes management system (AERx iDMS) delivers a liquid form of human insulin and is currently undergoing clinical studies in patients with type 1 and type 2 diabetes mellitus⁵⁶. The

delivery device includes a unique breath-guidance system that allows patients to breathe optimally and reproducibly. The drug is delivered to the lung only when the breathing is correct. This feature is not available in other aerosolized insulin products being developed. Since this system uses strips with liquid insulin, dosage adjustment is possible to the nearest unit, as is done with insulin injections. The bioavailability of insulin following the use of AERx iDMS is 13-17 per cent⁵⁷.

AIR particle technology (Alkermes): Other pulmonary insulin delivery systems under investigation include AIR particle technology (Alkermes in collaboration with Eli Lilly) and Technosphere. AIR particle technology uses a proprietary technology to prepare large porous microparticles. The density of the particles is less than 0.4 g/cm^3 , which allows particles over $5 \mu\text{m}$ in geometric diameter to deposit into the deep-lung region. In a recent study, human insulin inhalation powder (HIIP) delivered via AIR particle technology and an inhaler demonstrated the same rapid initial absorption and pharmacokinetic action and glucose lowering effect as subcutaneously administered lispro insulin. However, HIIP had a longer time-action profile than for SQ lispro (median time of return to baseline 480 vs 360 min)⁵⁸.

Technosphere insulin system: This system consists of an ordered lattice array of spherical particles and 18 per cent insulin formulated as a crystalline dry powder. The aerodynamic diameter of the particles is $0.4\text{-}5.8 \mu\text{m}$ ⁵⁷. With the development of a specific inhaler (the MedTone Inhaler) adapted to the physical properties of Technosphere/Insulin, the relative bioavailability compared to subcutaneously administered insulin was 50 per cent for the first 3 h and 30 per cent over 6 h^{57,59}.

The key benefit of inhaled insulin appears to be that patient satisfaction and quality of life are significantly improved, presumably due to the reduced number of daily injections required. However, the efficiency of inhaled insulin is lower

than that of subcutaneous injection because pulmonary delivery of insulin involves some loss of drug within the inhaler or mouth during inhalation. Due to the lower bioavailability of inhaled insulin, higher doses of inhaled insulin are required, and this may make it less cost-effective than injected insulin. In addition, since insulin is known to have growth-promoting properties [through its effects on the insulin-like-growth factor (IGF) receptor], a major concern among clinicians is the possibility of long-term effects from the intra-alveolar deposition of insulin within the lung. Thus, long term studies are needed to answer this question before inhaled insulin is widely prescribed and used.

Buccal insulin: Although inhaled insulin offers several advantages over the injected insulin, there are still some disadvantages and concerns mainly related to its long-term safety and tolerability. Buccal/oral insulin is one of many non-injectable forms of insulin that is being developed in an effort to find a painless, safe and effective alternative to insulin injections in treating diabetic patients.

Generex RapidMist: This device developed by Generex Biotechnology (Toronto, Canada) is a proprietary pressurized Metered Dose Inhaler (very similar to a small asthma inhaler) and is used to administer insulin to the buccal mucosa⁶⁰. The buccal insulin preparation (Oral-lyn™) is a human recombinant insulin (Humulin R) with added enhancers, stabilizers, and a non-chlorofluorocarbon propellant. The efficacy of buccal oral insulin has been demonstrated in a recent proof-of-concept study in 23 subjects with type 2 diabetes on multiple daily injections. In this open-label, cross-over, randomized study, the subjects received either 0.1 units/kg dose of SC insulin or 100 units Oral-lyn spray before a standardized meal. After 30 and 60 min, postprandial glucose levels were significantly lower with Oral-lyn compared with the injection treatment⁶¹. Longer term studies are currently underway with buccal insulin.

Oral insulin: Nobex Corp. (in joint pre-clinical development with Biocon India Limited) has developed hexylinsulin monoconjugate 2 (HIM2), in which a single amphiphilic oligomer is covalently linked to the free amino group on the Lys-[beta]29 residue of recombinant human insulin via an amide bond⁶². Compared with nonmodified insulin, HIM2 has alterations in physiochemical characteristics that resist enzymatic degradation and facilitate absorption when administered as an oral semisolid formulation in hard gelatin capsules. Since oral HIM2 is absorbed from the GI tract directly into the portal circulation, HIM2 may influence glucose levels primarily by suppressing hepatic glucose output in a manner similar to that of endogenous insulin. By mimicking the physiological mode of action, insulin therapy with oral HIM2 is expected to improve metabolic control without producing hyperinsulinaemia in the peripheral circulation. In a recent, randomized, single-blind, placebo-controlled study, Kipnes *et al*⁶³ demonstrated that single, oral doses of HIM2 (0.5 and 1.0 mg/kg) were safe, well tolerated and more effective than placebo and as effective as subcutaneous regular insulin (8 units) at controlling postprandial glycaemia in 18 patients with type 2 diabetes (mean BMI ~ 30 kg/m² and HbA1c ~ 8.6%). Improvements in glycaemia occurred even though peripheral insulin concentrations were lower following the administration of HIM2 (0.5 and 1.0 mg/kg) than subcutaneous insulin. The results of this study suggest that oral HIM2 may be useful in patients with type 2 diabetes who experience inadequate postprandial glycaemic control.

Another company which has developed technology to facilitate insulin absorption across the GI tract is Emisphere⁶⁴. Their Eligen® technology is a proprietary oral drug delivery technology based on the use of proprietary, synthetic chemical compounds known as EMISPHERE® delivery agents, or “carriers” which facilitate and enable the transport of therapeutic macromolecules (like insulin) across biological membranes such as the small intestine. In

phase I/II trials, Emisphere insulin tablets, acted rapidly and lowered the post-meal glucose levels, when administered to patients with type 2 diabetes shortly before a meal⁶⁴.

Transdermal insulin: A patch impregnated with insulin placed on the skin may be able to deliver a continuous low dose of basal insulin. However, since insulin is a large molecule, it does not permeate the skin easily. Several pharmaceutical and technology companies are developing transdermal delivery methods to facilitate insulin administration through the skin. Methods to increase the skin's permeability include sonophoresis (application of low-frequency ultrasound) and iontophoresis (application of a local electric current) to introduce the ions of a medication into the tissues. Altea Therapeutics is currently conducting phase 1 clinical trials in the USA for AT1391, the company's daily insulin skin patch designed to provide continuous basal levels of insulin for patients with diabetes. AT1391 incorporates a proprietary PassPort (TM) system, developed to deliver protein and peptide drugs, small-molecule drugs, genes and vaccines across the skin for local and systemic effect⁶⁵. Dermisonics is also developing a unique system for the non-invasive delivery of insulin and other large molecule drugs. This drug delivery system utilizes technologies developed in the field of sub-miniature, high-powered, ultrasonic devices and is coupled with a modified transdermal patch. The system enables insulin to penetrate the skin without the use of needles and the accompanying discomfort⁶⁶. Another company in the UK - Starbridge Systems is also investigating a patch containing a tiny pump (Starlet™), which delivers a three-day supply of insulin⁶⁷.

Although subcutaneous insulin administration has remained the route of choice for the last several decades, the inconvenience of multiple-injection regimens for diabetic patients desiring intensive management and the reluctance of patients with

poorly controlled type 2 diabetes mellitus to start insulin therapy have spurred the development of the above non invasive, needle-free delivery methods. It should be mentioned here that in selected and motivated patients, the use of continuous subcutaneous insulin infusion pumps is an option and may be beneficial in treating patients with type 2 diabetes mellitus who do not respond satisfactorily to more conventional subcutaneous insulin treatment regimens. However, continuous subcutaneous insulin infusion pumps are predominantly used in patients with type 1 diabetes and it is not expected that their use will become widespread in treating type 2 diabetics. On the other hand, with the rapid development of technology in this field, it is possible that in the future, subcutaneous administration of insulin may ultimately become outdated. Although inhaled insulin delivers effective doses of insulin in a less painful and more acceptable manner, with possibly improved patient compliance and better outcomes, longer term pulmonary safety data are still needed before inhaled insulin becomes an integral part of our therapeutic armamentarium. As regards other modes of insulin delivery - oral, buccal and dermal, more studies need to be performed to demonstrate the long-term safety, tolerability, and efficacy of these methods. Further, the initial high costs of these novel insulins will price them out of reach of the majority of people with type 2 diabetics across the world.

Another promising mode of insulin delivery is the intraperitoneal route. Intraperitoneal insulin delivery systems hold considerable promise because of their more physiologic delivery of insulin into the portal circulation and their ability to inhibit hepatic glucose production selectively, with less peripheral insulinaemia than with subcutaneous insulin injections⁶⁸. However, due to the invasive nature of their implantation into the abdominal cavity and the associated morbidity and costs, it is unlikely that this method will find widespread acceptance among patients with type 2 diabetes.

Latest continuous glucose monitoring devices

It is now well established that intensive therapeutic management with tight glycaemic control is associated with a significant reduction in serious diabetes-related complications and a decrease in the economic burden of this disease⁶⁹. However, the achievement of tight glycaemic control with intensive therapy requires frequent blood glucose monitoring. The ADA treatment guidelines recommend maintaining fasting serum glucose values within an optimal range of 90-130 mg/dl⁸. However, even with frequent daily self-monitoring of blood glucose, the achievement of consistent near normal glycaemia and the avoidance of hypoglycaemic and hyperglycaemic excursions remain elusive for many patients with diabetes. Also, frequent fingerstick blood glucose measurements only offer a static picture at any point and do not provide an idea of the magnitude and duration of glycaemic excursions. The recent availability of continuous glucose monitors provides an opportunity to match the demands of intensive therapy with intensive glucose monitoring. Data provided by these monitors can help identify periods of previously undetected nocturnal hypoglycaemia and postprandial hyperglycaemia and allow patients and clinicians to make specific changes in the timing and dosage of insulin, and dietary and physical activity alterations. Preliminary clinical evidence

among small patient groups with both type 1 and type 2 diabetes suggests that using continuous glucose monitoring system (CGMS) data to make therapeutic regimen adjustments results in an overall lowering of blood glucose values and a significant reduction in the frequency of glycaemic excursions⁷⁰. Further, the ability to achieve more consistent glycaemic control with continuous glucose monitoring may even translate into a reduction in health care costs⁷¹.

There are several CGMS devices available in the USA. These include the Continuous Glucose Monitoring System Gold (CGMS Gold; Medtronic MiniMed), the GlucoWatch G2 Biographer (Cygnus) and The Guardian® RT Continuous Glucose Monitoring System (Medtronic MiniMed). Devices in development include the FreeStyle Navigator Continuous Glucose Monitor (Abbott Laboratories) and the Pendra (Pendragon Medical, Zurich, Switzerland)⁷².

CGMS Gold: The CGMS Gold was the first system to be introduced in 1999 and approved for use by healthcare professionals to view comprehensive glycaemic patterns that cannot be captured using traditional finger sticks or HbA1c measurements. The system (Fig. 1) contains two key components: a subcutaneous glucose sensor and a small, pager-type monitor⁷³. The glucose sensor is inserted into the



Fig. 1. Minimed medtronic gold continuous glucose monitoring system.

patient's subcutaneous tissue, usually in the abdominal area and is worn for a period of 24 to 72 h while a patient goes about his/her daily activities. During this time, the sensor measures glucose in subcutaneous fluid every 10 seconds and stores the average of 30 measures obtained over 5 min. CGMS calibration requires that traditional blood glucose testing be performed at the time of application and at least 4 times daily for the rest of the test period. Without such calibration, CGMS readings may be inaccurate. Glucose data and event information entered manually by the patient are stored in the monitor. After 3 days of recording, data from the monitor are downloaded to a computer for retrospective analysis. Thus this device does not display glucose readings in real time, but only retrospective glucose readings for downloading and analysis by healthcare providers. On the other hand, the Guardian RT system, recently approved by the U.S. Food and Drug Administration for patients over the age of 18 yr with type 1 and type 2 diabetes, is a CGMS device that displays an updated real time glucose value every five minutes and even alerts patients when glucose levels become too high or too low, thus helping patients take action before they experience a problem⁷³.

Guardian® RT CGMS: The recently approved Minimed Medtronic Guardian RT (Real Time) System has 3 components: a glucose sensor, a transmitter and a monitor. The glucose sensor is connected to a transmitter and both attach to the skin by an adhesive patch. The sensor measures glucose values from interstitial fluid and converts this into an electronic signal which the transmitter sends to the monitor every five minutes. The transmitter has a battery lifespan of approximately one year with near continuous sensor use (the sensor itself needs to be changed every 72 h). By sounding an alarm (or vibrating), the monitor alerts patients to potentially dangerous high or low glucose levels. To calibrate the system, a minimum of two fingerstick glucose meter measurements are entered into the monitor each day (every 12 h). A fingerstick glucose meter measurement is also required to confirm high or low sensor values prior to making a self-management decision (*i.e.*, increase or decrease in insulin dose). The monitor should not be exposed to water: however, patients can easily shower or bathe without interrupting their glucose data since the monitor will receive a signal as long as it is within six feet of the transmitter⁷³.



Fig. 2. Gluowatch biographer.

The GlucoWatch2 Biographer: The GlucoWatch2 Biographer (Cygnus, Redwood City, California) was the first frequent monitoring device to report real-time glucose values to patients throughout the day or night for up to 13 h. This device consists of two integrated parts, the biographer and the autosensor (Fig. 2). The biographer is a small, wristwatch-like device that is worn on the forearm and contains sampling and detection technology, electronic circuitry, and a digital display. Three separate technologies are incorporated into the GlucoWatch Biographer: glucose sample extraction through reverse iontophoresis, glucose sample measurement by amperometric biosensor, and data verification and conversion using an algorithm leading to the display of the glucose reading⁷³. The Biographer provides 13 h of glucose readings as

often as every 10 min. The readings are the time-averaged measurements of the value 10 min earlier and the current value. An advantage of the Biographer is its ability to determine glucose patterns and trends and display real-time glucose values. It also has an alarm to alert the user if it is predicted that the value will be below the low-alarm level in the next 20 min. Problems with the Biographer include missed glucose readings due to excessive perspiration (which is of concern because perspiration can be a symptom of hypoglycaemia) and mild-to-moderate skin irritation. As with the Medtronic MiniMed CGMS, although the GlucoWatch Biographer is accurate enough to detect trends, the accuracy is not as good as current-day glucose meters⁷³. In one home study, use of the GlucoWatch resulted in improved hypoglycaemia

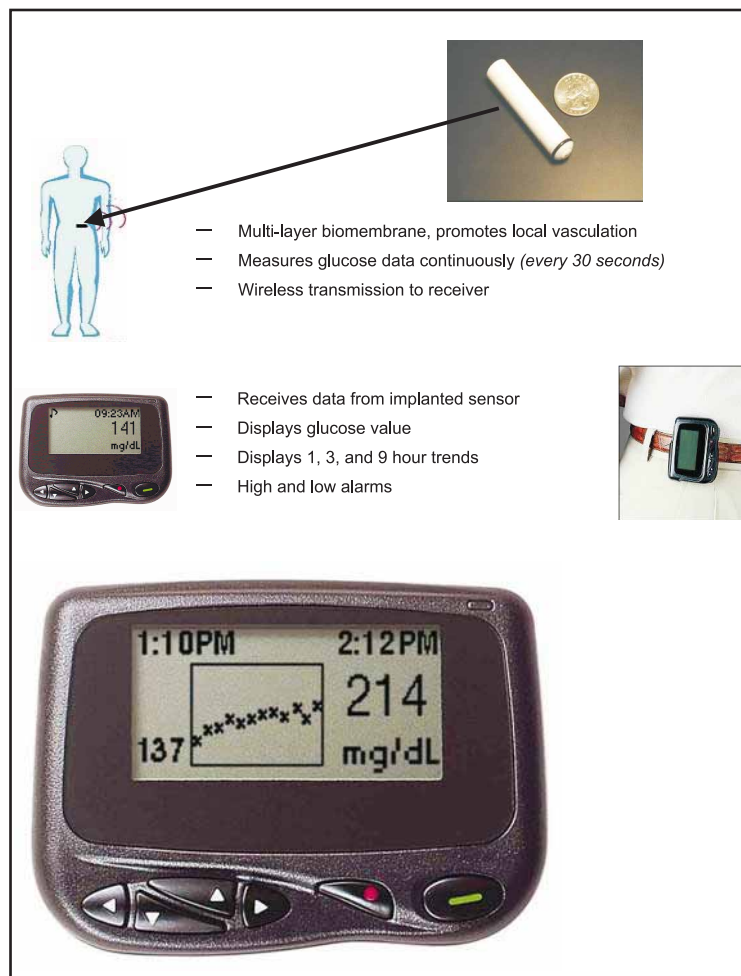


Fig. 3. The DexCom continuous glucose monitor system.

detection and improved Hb A1c levels⁷⁴. However, in another study, use of the GlucoWatch Biographer in addition to standard glucose monitoring, did not improve glycaemic control or reduce the frequency of severe hypoglycaemia. In this study skin reactions and other problems also led to decreasing sensor use over time⁷⁵.

DexCom continuous glucose monitor system: In contrast to the above systems in which the sensors are placed subcutaneously for up to 72 h, in the DexCom Continuous Glucose Monitor System, the sensor is implanted in an abdominal pouch for longer periods of several months. The sensor is a small cylinder about the size and shape of an AA battery and contains a battery, an integrated circuit, a radio transmitter, and a biosensor covered with a multilayered membrane (Fig. 3)^{73,76}. The sensor which is implanted in the subcutaneous tissue of the abdomen by a surgeon in an outpatient procedure under local anaesthesia, samples glucose levels continuously (every 30 seconds) from interstitial fluid in subcutaneous tissue and wirelessly transmits data (glucose values) to a receiver every 5 min. After the implantation procedure, patients are advised to restrict their activities for 2 wk. The receiver is an externally worn pager-sized device that displays the glucose values every 5 min. The data are displayed in real time on the receiver either as a number, or as glucose trends. In a recent clinical trial, the use of data from a long-term, implanted, real-time continuous glucose sensor helped patients reduce hyperglycaemic excursions without increasing the risk of hypoglycaemia⁷⁶. The Dexcom implantable CGMS is not yet approved for clinical use.

Other continuous glucose monitoring systems in development include the Sensys Medical device (Chandler, Arizona) which measures blood glucose non invasively through the use of near-infrared (NIR) spectroscopy and the Pendra continuous glucose monitoring device using impedance spectroscopy^{73,77}.

Despite the availability of CGMS, these devices are not for routine use in patients with diabetes. Proper patient selection is essential to ensure safe use of CGMS. Patients should be motivated to participate in their diabetes care, mechanically adapt and receive adequate diabetes education. It is important to note that currently available CGMS devices that provide real-time readings should not be used to make therapeutic decisions because they are not sufficiently accurate. Instead, an abnormal reading should prompt a finger-stick blood glucose measurement to make a therapeutic decision. Ultimately, as methods for minimally invasive and non invasive continuous monitoring improve, it is expected that CGMS will become a routine part of diabetes management, initially for patients with difficult-to-control diabetes and eventually for most patients with diabetes⁷⁸. In the not too distant future, it may even be possible to envisage a fully automated glucose-control machine - "an electronic pancreas", with an implantable long-term CGMS device continuous monitoring blood glucose levels and transmitting this to an implanted intraperitoneal pump which continuously delivers insulin into the portal circulation.

Update on diabetes prevention

As already mentioned, diabetes currently affects an estimated 171 million individuals and is a major cause of morbidity and mortality worldwide. With a projected doubling of the number of global cases of diabetes by 2030¹, the development of effective strategies to prevent diabetes is of paramount importance.

Recent evidence obtained from randomized, controlled trials in patients with pre-diabetes/impaired glucose tolerance from across the world [China (Da Qing study), Finland (Finnish Diabetes Prevention Study) and the USA (Diabetes Prevention Program)] has definitively established that the achievement and maintenance of modest weight loss of about 3 to 5 kg (7 to 10 lbs) through sustained life style interventions

with diet and physical activity reduces the incidence of type 2 diabetes in high risk persons by up to 58 per cent over 3 to 4 yr⁷⁹⁻⁸¹. Life style modification may also significantly reduce the incidence of diabetes in the absence of weight loss. In a recent study of Asian Indians from Chennai, India⁸², Ramachandran *et al* randomized 531 (421 men 110 women) subjects with impaired glucose tolerance (mean age 45.9 ± 5.7 yr, BMI 25.8 ± 3.5 kg/m²) into four groups: group 1 (control), group 2 (life style modification), group 3 (metformin) and group 4 (life style advice + metformin). After 3 yr, the cumulative incidence of diabetes was 55 per cent in the untreated control group and compared to the control group, there was a relative risk reduction of 28.5 per cent with lifestyle measures, 26.4 per cent with metformin and surprisingly only 28.2 per cent with lifestyle + metformin. Thus, there was no synergistic effect of combining metformin and life style. It is important to note that the rate of progression from impaired glucose tolerance to diabetes in this study (55% over 3 yr in the control group in this study) is extremely high as compared to the US Diabetes Prevention Program where the estimated cumulative incidence of diabetes at 3 yr was only 28.9 per cent in the control group. Also of note is the fact that, in the intensive life style group, despite dietary and exercise modifications and a reduction in diabetes incidence, there was no decrease in weight, but rather a significant increase in weight (<1 kg) from baseline at 24 months. Thus the beneficial effects of life style modifications in this population appear to be independent of weight loss. As regards the weight in the other groups, in the control group there was a significant increase in weight (<1 kg) at annual follow up and in the metformin alone and metformin + life style groups, there were no significant differences in weight as compared with baseline values⁸².

In addition to reducing the progression to diabetes in subjects with impaired glucose tolerance, life style modification with diet and exercise also has beneficial effects on the entire

cardiovascular risk profile as well as non cardiovascular benefits related to weight loss and an improved diet that may eventually reduce the risk of cardiovascular disease^{81,83}. However, despite the encouraging results of life style measures in the above studies, long-term adherence to life style modification (diet and exercise) and feasibility of implementation in a non study setting are potentially limiting factors to widespread implementation of such programmes. Thus, pharmacological therapy to prevent type 2 diabetes may be an important therapeutic modality in those patients in whom life style interventions fail or are not feasible. Among the several pharmacologic agents studied, oral hypoglycaemic agents and orlistat are the only drugs that have been studied in randomized controlled trials with diabetes incidence as the primary end point. In these studies of 2-4 yr duration, as compared to placebo, metformin was associated with a 31 and 26 per cent decreased incidence of diabetes in the US Diabetes Prevention Program¹⁷ and Indian Diabetes Prevention Program respectively⁸²; acarbose was associated with a 25 per cent decreased incidence in the STOP NIDDM study⁸⁴, troglitazone with a 55 per cent decreased incidence in the US Diabetes Prevention Program⁸⁵ and orlistat with a 37 per cent decreased incidence of diabetes compared to placebo in the XENDOS study⁸⁶.

In contrast to the above studies, in which the primary end point was the prevention of diabetes, there have been several other studies with non diabetic agents in which post-hoc analyses have reported a reduction in the incidence of diabetes⁸⁷. The major antihypertensive drug classes appear to exert differing effects on diabetes incidence. While thiazide diuretic and beta-blockers are potentially diabetogenic and calcium channel blockers appear neutral, the ACE inhibitors and ARBs may reduce diabetes incidence (ramipril in the HOPE study, valsartan in the VALUE study and candesartan in

the CHARM study)⁸⁸. Four post-hoc analyses of placebo-controlled statin trials reported conflicting results regarding the effect of statin therapy on diabetes incidence⁸⁷. In the West of Scotland Coronary Prevention Study (WOSCOPS), diabetes incidence was significantly lower with pravastatin treatment⁸⁹. However, in three other studies, there did not appear to be any protective effect of statins on diabetes incidence: the Heart Protection Study (simvastatin)⁹⁰, the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study (pravastatin)⁹¹ and the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) study (atorvastatin)⁹². As regards fibrates, in a post hoc analysis from the Bezafibrate Infarction Prevention (BIP) trial, bezafibrate therapy was associated with a reduction in diabetes incidence from 54 to 42 per cent compared with placebo⁹³. There also appears to be a protective effect of hormones in the prevention of diabetes. In a post-hoc analysis of the Heart Estrogen/ Progestin Replacement Study (HERS), combination of estrogen and progesterone therapy was associated with a significant reduction in the incidence of diabetes from 9.5 to 6.2 per cent compared with placebo⁹⁴. Several other studies are currently in progress to determine if the use of other anti-diabetic agents will prevent or delay the onset of type 2 diabetes. These include the NAVIGATOR study with nateglinide and valsartan⁹⁵, the DREAM study (ramipril and rosiglitazone)⁹⁶, the ACTOS NOW study (pioglitazone) and the ORIGIN study (insulin glargine)⁹⁵.

The scientific evidence supporting primary prevention of diabetes by life style intervention and pharmacologic agents is strong and growing. However, currently it is unclear whether a short-term delay in the biochemical diagnosis of diabetes is a useful surrogate end point and whether the effects of drug therapy are sustained, cost-effective, and free

of serious adverse effects in the longer term. Further, the costs and benefits of achieving primary prevention of diabetes by life style and pharmacologic means need proper analysis and careful consideration by the makers of health policy worldwide.

Conclusion

The prevention and control of the diabetes pandemic and its complications is a major public health challenge. But there is hope for the future. The progress of research in all fields of diabetes therapeutics from diabetes treatment to continuous glucose monitoring systems to novel insulin delivery systems has been spectacular. These advances have resulted in newer pharmacologic agents, implantable glucose sensors and inhaled insulin. There is also hope that large scale implementation of intensive life style programmes and education efforts may help to prevent diabetes in high risk individuals. Indeed, the repertoire of options and strategies currently available (and in the pipeline) to treat and prevent/delay diabetes and its complications is impressive. It remains to be seen if we are able to practically implement these therapeutic strategies so that we can prevent or ameliorate the enormous health burden and economic costs associated with diabetes⁹⁷.

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