Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized and overproduced, leading to hyperglycemia. Diabetes is a common disease. The current worldwide prevalence is estimated to be approximately 250 million and is expected to reach 380 million by 2025. The worldwide costs of diabetes in 2007 were approximately $232 billion and are likely to be $302 billion by 2025. The mean annual per capita healthcare costs for an individual with diabetes are approximately 2.3-fold higher than those for individuals who do not have diabetes. It is the fourth most common cause of death in the developed world.

**ETIOLOGY**

There are genetic and environmental components that affect the risk of developing either type 1 or type 2 DM. A positive family history of type 2 DM is predictive for the disease. Studies of identical twins show 70% to 80% concordance for developing type 2 DM. Furthermore, there is a high prevalence of type 2 DM in offspring of parents with the disease (up to 70%) as well as in siblings of affected individuals. Persons more than 20% over their ideal body weight also have a greater risk of developing type 2 DM. Type 1 DM results from autoimmune beta cell destruction, and most, but not all, individuals have evidence of islet-directed autoimmunity.

**CRITERIA FOR DIABETES DIAGNOSIS**

As per ADA 2011 guidelines, any one of the following can be used for diagnosis of diabetes:

1. HbA1C ≥ 6.5%.
2. FPG ≥ 126 mg/dl (7.0 mmol/l). (Fasting: no caloric intake for at least 8 h).
3. 2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).

**TREATMENT OF TYPE 2 DIABETES MELLITUS**

1. Non-pharmacological measures
   
The patient with type 1 or type 2 DM should receive education about nutrition, exercise, care of diabetes during illness, and medications to lower the plasma glucose.

   Nutrition

   *Medical nutrition therapy* (MNT) is a term to describe the optimal coordination of caloric intake with other aspects of diabetes therapy (insulin, exercise, weight loss). Primary prevention measures of MNT are directed at preventing or delaying the onset of type 2 DM in high-risk individuals (obese or with prediabetes) by promoting weight reduction. Hypocaloric diets and modest weight loss (5–7%) often result in rapid and dramatic glucose lowering in individuals with new-onset type 2 DM (Table 1).
In patients with diabetes, the ADA recommends 150 min/week (distributed over at least 3 days) of moderate aerobic physical activity. The exercise regimen should also include resistance training. Exercise has multiple positive benefits including cardiovascular risk reduction, reduced blood pressure, maintenance of muscle mass, reduction in body fat, and weight loss.

Following drug groups can be useful for treatment of T2DM:

### A. Biguanides

Metformin is the only drug of this class presently available. It is considered first line drug for treatment of T2DM. Currently proposed mechanisms of action include (1) reduced hepatic and renal gluconeogenesis; (2) slowing of glucose absorption from the gastrointestinal tract, with increased glucose to lactate conversion by enterocytes; (3) direct stimulation of glycolysis in tissues, with increased glucose removal from blood; and (4) reduction of plasma glucagon levels.

Metformin lowers hemoglobin A1c values by about 2%. Metformin does not promote weight gain and can reduce plasma triglycerides by 15% to 20%. There is a strong consensus that reduction in hemoglobin A1c by any therapy (insulin or oral agents) diminishes microvascular complications. Metformin is the only therapeutic agent that has been demonstrated to reduce macrovascular events in type 2 DM.

### B. Sulfonylurea

Sulfonylureas bind and block the ATP-sensitive K+ channel. The administration of sulfonylureas to type 2 DM patients increases insulin release from the pancreas. Sulfonylureas also may further increase insulin levels by reducing hepatic clearance of the hormone. The first generation of sulfonylureas includes tolbutamide, acetohexamide, tolazamide, and chlorpropamide. A second, more potent generation of sulfonylureas includes glyburide (glibenclamide), glipizide, gliclazide, and glimepiride.

### C. Thiazolidinediones

Thiazolidinediones are selective agonists for nuclear peroxisome proliferator-activated receptor (PPAR) gamma. These drugs bind to PPAR gamma, which activates insulin-responsive genes that regulate carbohydrate and lipid metabolism. Thiazolidinediones increase glucose transport into muscle and adipose tissue by enhancing the synthesis and translocation of specific forms of the glucose transporters. Pioglitazone is the only drug from this group which is currently available in market.

### D. α-Glucosidase Inhibitors

α-Glucosidase inhibitors reduce intestinal absorption of starch, dextrin, and disaccharides by inhibiting the action of α-glucosidase in the intestinal brush border. Inhibition of this enzyme slows the absorption of carbohydrates; the postprandial rise in plasma glucose is blunted in both normal and diabetic subjects. The α-Glucosidase inhibitors do not stimulate insulin release and therefore do not result in hypoglycemia. These drugs are mainly used to reduce post-prandial hyperglycemia. Acarbose and voglibose are commonly used drugs in this group.

### E. Meglitinide

Like sulfonylureas, meglitinides stimulate insulin release by closing ATP-dependent potassium channels in pancreatic Beta cells. They are short acting drugs and used for reducing postprandial glycemic elevations in type 2 DM patients. Repaglinide and nateglinide are the available drugs from this group.

### F. Insulin

Insulin is generally used in T2DM when oral drug therapy could not achieve the glycemic goals. Preparations of insulin can be classified according to their duration of action into short, intermediate, and long acting and by their species of origin: human or porcine. Human insulin is now most commonly used (Table 2).

### NEWER DRUGS FOR TREATMENT OF T2 DIABETES MELLITUS

1. GLP-1 Analogues

Glucagon like peptide-1 (GLP-1) is a 30-amino acid gut hormone secreted in a nutrient-dependent manner.
that stimulates insulin secretion and inhibits glucagon secretion and gastric emptying, resulting in reduced postprandial glycemia.\(^{10}\) GLP-1 is a member of the pro-glucagon incretin family and has insulinomimetic, insulinotropic, and antiapoptotic properties.\(^{11}\) In individuals with normal glucose tolerance, the ingestion of glucose involves a much larger insulin response than observed after an isoglycemic intravenous glucose infusion. This enhancement in insulin secretion called the “incretin” effect is markedly reduced to >50% in patients with diabetes compared with individuals with normal blood glucose. The incretin effect is mediated by the intestinal secretion of 2 hormones, glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. The two incretins differentially stimulate insulin secretion. GIP has little effect on augmenting insulin secretion in type 2 DM, whereas GLP-1 significantly augments glucose-dependent insulin secretion. GLP-1 concentrations are often reduced in type 2 diabetes, but biological potency is mostly retained, making GLP-1 an attractive target for development of treatment. But, circulating GLP-1 is rapidly (1 to 2 minutes) inactivated by the dipeptidyl peptidase IV enzyme (DPP-IV).

Exenatide has a 53% amino acid sequence similarity to human GLP-1.\(^{15}\) Clinical trials have demonstrated a reduction in both fasting and postprandial glucose concentrations, a 1–2% reduction in HbA1c concentrations.\(^{16,17}\) Exenatide therapy also caused weight loss in patients with type 2 diabetes, in addition to its beneficial effects on glycaemic parameters. In a variety of clinical studies, a significant loss in body weight of 1.5–3.0 kg was observed after 30 weeks. This effect continued and led to a further weight loss of 5.3 kg after 3 years.\(^{18}\) Surrogate parameters for b-cell function also improved with exenatide treatment in clinical studies. The insulin secretion rate, HOMA B (homeostatic modelling assessment of b-cell function) and the proinsulin/insulin ratio changed in a favourable way. Additionally, the first phase of insulin secretion, which is already lost in the early stages of type 2 diabetes, is restored under treatment with exenatide when examined with an intravenous glucose tolerance test.\(^{19}\)

Side-effects of exenatide include nausea and less commonly, vomiting or diarrhoea, particularly when starting therapy. Exenatide has no intrinsic risk for increasing the incidence of hypoglycaemia. However, hypoglycaemic events were frequently observed only in patients treated with exenatide in combination therapy with a sulfonylurea, but then the hypoglycaemic episodes were caused by the sulfonylurea treatment. Therefore, it is suggested that the sulfonylurea dose is reduced when starting exenatide combination therapy. It is recommended that treatment is initiated with a dose of 5 mg twice daily which may be increased to 10 mg twice daily approximately 1 month later.

Liraglutide

Liraglutide is the first human GLP-1 analogue with two modifications in the amino acid sequence of native human GLP-1 and an attachment of a fatty acid side chain to the peptide. With a biological half life of approximately 13.5 hours, it is suitable for once-daily subcutaneous injections.\(^{20}\) It is not excreted by the kidneys, and is not subjected to DPP-4 degradation.\(^{21}\) It provides greater improvements in glycaemic control, induces weight loss, improves obesity-related risk factors, and reduces pre-diabetes. It is also associated with reductions in HbA1c and blood pressure.\(^{22}\)

In a 2-year study of patients with newly diagnosed type 2 diabetes, liraglutide as monotherapy led to a sustained and stable HbA1c reduction of 0.9% at a dose of 1.2

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**Table 2 : Types of conventional insulins and their action duration**

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therapeutic goals with their current oral medication.\(^{13}\) A slow-release formulation for once weekly administration is presently finalizing the approval process after completing important clinical phase III studies.\(^{14}\)
mg and 1.1% at a dose of 1.8 mg once daily. The Liraglutide Effect and Action in Diabetes (LEAD) program consisted of a series of phase 3 studies that investigated liraglutide use as monotherapy or in combination with metformin, metformin plus rosiglitazone, or metformin plus a sulfonylurea versus placebo and active comparators. In a direct head-to-head comparison with the DPP-4 inhibitor sitagliptin, liraglutide was superior in lowering glycaemic parameters and body weight at both doses of 1.2 mg/day and 1.8 mg/day. The corresponding HbA1c changes were -1.50% (95% CI -1.63, -1.37) for liraglutide 1.8mg and -1.24% (95% CI -1.37, -1.11) for liraglutide 1.2 mg compared with sitagliptin (-0.90%, 95% CI -1.03,-0.77). Significant weight reductions versus placebo were observed with liraglutide in combination with metformin, metformin plus rosiglitazone, and metformin plus a sulfonylurea. These studies also provided evidence of the efficacy of liraglutide to achieve good glycemic control over the medium (26 weeks) and long terms (52 weeks), and of clinically meaningful reductions in body weight and systolic blood pressure achieved with liraglutide treatment.

Gastrointestinal adverse effects were also common in clinical studies with liraglutide; however, in a direct head-to-head study, nausea and vomiting were less frequent with liraglutide and presented for a shorter period at the beginning of therapy than with exenatide. Animal studies have shown an increased occurrence of thyroid medullary cancer with high doses of liraglutide but the clinical relevance of this work is unclear. Early clinical trials of liraglutide suggested an increased incidence of pancreatitis.

Other Long-Acting GLP-1 Receptor Agonists in Development

Albiglutide

It is a human GLP-1 receptor agonist with two molecules of GLP-1 linked to albumin. The biological half life is around 5 days, which makes once-weekly dosing feasible for albiglutide. In clinical phase II studies, albiglutide has been tested in a dosage range from 4mg given once weekly to 100 mg once monthly. The HbA1c reductions (from a baseline of 8.0%) observed after 16 weeks of therapy were similar for the dosages 30mg weekly, 50mg bi-weekly and 100mg monthly (-0.87%, -0.79% and -0.97%, respectively).

Lixisenatide

A GLP-1 agonist, as a once-daily monotherapy is being assessed in the GetGoal-M-As phase 3 clinical trial program, which started in May 2008 and has enrolled 4,500 patients. Lixisenatide had been demonstrated to improve glycemic control and promote weight loss in 361 patients with type 2 diabetes during a 12-week, randomized, double-blind, multicenter phase 3 trial.

Tasgoglutide

It has 93% homology to endogenous GLP-1. A long-acting profile was obtained by making 2 amino acid substitutions and using a sustained-release formulation. Subcutaneously administered taspoglutide was associated with glucose-lowering effects at dosing intervals of up to 14 days in 2 clinical studies. Taspoglutide has entered Phase III clinical development as a once-weekly therapy.

2. DPP-4 inhibitors

The effects of endogenous incretins are short-lived because of rapid degradation and inactivation by the enzyme DPP-4. Inhibitors of DPP-4 have been developed to prevent the inactivation of GLP-1 and prolong the activity of the endogenously released hormone. In contrast to GLP-1 receptor agonists, these drugs are available orally and have a longer duration of action, requiring only once daily dosing. They are effective at controlling hyperglycaemia, reducing HbA1c concentrations by around 1%, improving pancreatic β-cell function, and can be used as monotherapy or in combination with other agents.

Sitagliptin

A selective DPP-4 inhibitor was approved in 2006 by the FDA as the first oral incretin enhancer for use as monotherapy or in combination with metformin or thiazolidinedione. Sitagliptin exhibits high inhibitory potency against DPP-4 in vitro (IC50 = 18 nM) and is (>1000-fold) selective for DPP-4 versus its homologues DPP-8 and DPP-9. In clinical trials of sitagliptin, reductions in HbA1c were seen with combination therapy with metformin and with monotherapy. Cleared primarily renally; reduce dosage in patients with moderate or severe renal impairment (CrCl _50 mL/min). At 24 hours after administration, plasma DPP-4 activity was inhibited by 47% with sitagliptin 25 mg and by 80% with sitagliptin 200 mg compared with placebo. In a monotherapy study, 521 patients were randomly assigned to receive sitagliptin 100 mg once daily, sitagliptin 200 mg once daily, or placebo for 18 weeks. HbA1c was decreased by 0.48% with sitagliptin 100 mg and by 0.36% with sitagliptin 200 mg, reductions that were both significant compared with the 0.12% increase with placebo (both, P<0.001). FPG was increased by 7 mg/dL with placebo compared with reductions of 13 mg/dL.
with sitagliptin 100 mg (P < 0.001) and 11 mg/dL with sitagliptin 200 mg (P < 0.01).32

In a double-blind trial, 701 patients with T2DM and inadequate glycemic control (HbA1c, 7%–10%) during monotherapy with metformin at a dose of 1500 mg/d were randomly assigned to receive additional administration of sitagliptin 100 mg/d or placebo for 24 weeks.141 Sitagliptin was associated with significantly greater reductions from baseline in HbA1c (0.67% vs. 0.02%) and FPG (16 vs. 9 mg/dL) compared with placebo (both, P < 0.001). The incidences of hypoglycemia were 1.3% with sitagliptin and 2.1% with placebo.33

The Sitagliptin Cardiovascular Outcome Study (TECOS) is a long-term CV outcomes trial evaluating the impact of sitagliptin on composite CV endpoints including CV-related death, nonfatal MI, and nonfatal stroke. TECOS began recruiting participants in December 2008. An estimated 14,000 patients will be recruited, with results expected approximately in 2014.34

Vildagliptin

Vildagliptin, which, like saxagliptin, is a cyanopyrroli-dine compound and an inhibitor of the DPP-4 enzyme.35 Vildagliptin exhibits higher selectivity for DPP-4 (IC50, 0.1 uM) in vitro compared with other peptidases. Vildagliptin had a rapid absorption profile, with the oral dose exhibiting a Tmax of 1.5 hours and a Cmax of 245 ng/mL. The t1/2 was 2.13 hours and the AUC0–∞ was 1100 ng/mL/h with the oral dose. Its dose is 50mg twice daily (morning and evening) when used in dual combination with metformin or a thiazolidinedione; 50mg once daily in the morning when used in dual combination with a sulphonylurea.

A smaller (N=354 patients), 24-week study of vildagliptin 50 to 100 mg/d as monotherapy yielded significant HbA1c reductions from baseline versus placebo, ranging from −0.5% to −0.8% compared with placebo (0%) (all, P <0.011).37

In a randomized, double-blind, 24-week study, 544 patients with an HbA1c of 7.5% to 11.0% during stable metformin treatment (1500 mg/d) received random assignment to additional administration of vildagliptin 50 mg once daily, vildagliptin 50 mg BD, or placebo. The improvements from baseline in HbA1c with vildagliptin 50 mg once daily (-0.5%) and 50 mg BD (-0.9%) were significant compared with the deterioration in HbA1c (-0.2%) seen with placebo (both, P < 0.001). Compared with the increase in FPG observed with placebo (-13 mg/dL), vildagliptin 50 mg once daily (-2 mg/dL; P <0.003) and 50 mg BD (-18 mg/dL; P < 0.001) were associated with significant improvements.

The reduction from baseline in diastolic blood pressure with vildagliptin 100 mg/d (~2.0 mm Hg) was significantly greater than with placebo (~0.3 mmHg) (P=0.0343).

The adverse events with vildagliptin are rare cases of hepatic dysfunction (including hepatitis). ALT or AST elevations ≥3x ULN for Vildagliptin 50mg od (0.2%), Vildagliptin 50mg bd (0.3%) compared to 0.2% with comparators in clinical trials.

Saxagliptin

The inhibitory potency of saxagliptin for DPP-4 in vitro is 400-fold greater than for DPP-8 and 75-fold greater than for DPP-9. Compared with sitagliptin or vildagliptin, saxagliptin is at least 10-fold more potent and inhibitor of DPP-4.38 It is metabolized by CYP3A4 enzyme and can have drug interaction with multiple drugs.

In a randomized, double-blind study of saxagliptin added to a regimen of metformin, 743 patients with HbA1c 7% to 10% during monotherapy with metformin 1500 to 2500 mg/d received additional administration of saxagliptin 2.5, 5, or 10 mg/d or placebo for 24 weeks.19 Changes in HbA1c with saxagliptin 2.5 mg (-0.59%), 5 mg (-0.69%), and 10 mg (-0.58%) were significant relative to placebo (+0.13%) (all, P < 0.0001). Changes in FPG with saxagliptin 2.5 mg (-14.3 mg/dL), 5 mg (-22.0 mg/dL), and 10 mg (-20.5 mg/dL) were also significant compared with that observed with placebo (-1.2 mg/dL) (all, P <0.0001), and the incidences of hypoglycemia were<1% in all 4 treatment groups.

A study of saxagliptin added to sulfonylurea therapy enrolled patients with inadequate glycemic control (HbA1c, 7.5%–10%) during treatment with a submaximal dose of a sulfonylurea.40 Patients were placed on treatment with glyburide 7.5 mg, and those with inadequate response (HbA1c, ≥7.0%; mean FPG, ≥140 mg/dL; and/or mean fasting whole blood glucose, ≥131 mg/dL; N=768) were randomly assigned to receive adjunctive saxagliptin 2.5 mg, adjunctive saxagliptin 5 mg, or placebo once daily plus uptitrated glyburide. Improvements from baseline in HbA1c were significantly greater with saxagliptin 2.5 mg (-0.54%) and 5 mg (-0.64) compared with placebo (+0.08) (both, P =0.0001). Improvements in FPG were also significantly greater with saxagliptin 2.5 mg (-7 mg/dL; P =0.0218) and 5 mg (-10 mg/dL; P = 0.0020) compared with placebo (+1 mg/dL). Reductions ranging from -3.2 to -3.9 mm Hg in systolic
blood pressure and -1.8 to -3.3 mm Hg in diastolic blood pressure occurred in saxagliptin treated patients.

Common adverse events with saxagliptin are: Headache (7%), Sinusitis (3%), Abdominal pain, gastroenteritis, vomiting (2%), and UTI (7%).

Other DPP-IV inhibitors

Alogliptin
The quinazoline-based compound alogliptin is a potent (IC50, 6.9 nM) inhibitor of DPP-4 in vitro. In a randomized, double-blind study in 500 patients with inadequate glycemic control while receiving sulfonylurea monotherapy, treatment with alogliptin 12.5 mg, alogliptin 25 mg, or placebo was added for 26 weeks. The HbA1c reductions from baseline with alogliptin 12.5 mg (-0.39%) and 25 mg (-0.53%) were significant compared with the change seen with placebo (+0.01%) (both, \( P < 0.001 \)). Alogliptin is under regulatory review by the FDA, which has requested that the manufacturer conduct an additional cardiovascular safety trial.

Linagliptin
It is the latest DPP-IV inhibitor to be approved by US-FDA. It shows highly selective, potent, dose-dependent inhibition of DPP-4, with >80% inhibition of DPP-4 throughout the 24-hour dosing interval. Its recommended dose is 5 mg once a day.

In two double-blind, multicentre trials (n >350 evaluable patients/trial) in adult patients with inadequately controlled type 2 diabetes mellitus, oral linagliptin monotherapy (5 or 10mg once daily) was significantly more effective than placebo in improving glycaemic control and several parameters of pancreatic function, with placebo-corrected adjusted mean changes in glycosylated haemoglobin (HbA1c) levels of -0.69% to -0.88% after 12 or 24 weeks. Linagliptin 5 or 10mg once daily was also significantly more efficacious than voglibose 0.2 mg three times daily in terms of improving glycaemic control in a 26-week, double-blind, multicentre trial.

3. Newer Insulins

Insulin detemir
It is a basal insulin analog that provides effective therapeutic options for patients with type 1 and type 2 diabetes. Insulin detemir is a soluble derivative of human insulin in which the threonine residue at position B30 of the human insulin molecule has been removed and a 14-carbon fatty acid side-chain has been attached to position B29. Clinical studies have demonstrated that detemir is responsible for significantly lower within-subject variability and no or less weight gain than NPH insulin and glargine. Insulin detemir has consistently been shown in randomized, controlled trials to have a weight-sparing effect in both type 1 DM and type 2 DM.

The long-term efficacy and safety of insulin detemir compared to NPH insulin was examined in a 2-year, randomized, controlled trial in patients with type 1 DM using a treat-to-target basal-bolus regimen with insulin aspart. In this study, 22% of patients treated with insulin detemir reached a HbA1c # 7.0% in the absence of confirmed hypoglycemia during the last month of treatment vs. 13% on NPH insulin (\( P = 0.02 \)). Detemir was associated with a 69% lower risk of major hypoglycemic episodes compared to NPH (\( P < 0.001 \)). The risk of nocturnal hypoglycemia was 46% lower with detemir than with NPH (\( P=0.001 \)). Moreover, patients treated with detemir gained less weight (detemir 1.7 kg, NPH 2.7 kg; \( P = 0.02 \)).

Insulin Glulisine
Insulin glulisine is a human insulin analogue altered by replacing asparagine with lysine at position B3 and by replacing lysine with glutamic acid at position B29, forming 3B-lysine-29Bglutamic acid-human insulin. It is a rapid acting insulin analogue. It has similar binding properties, and is associated with a faster onset but similar level of glucose disposal, to regular human insulin (RHI).

Several well designed trials have investigated the efficacy of insulin glulisine (with and without basal insulin) versus comparator agents (with and without basal insulin) in patients with type 1 and type 2 diabetes. In patients with type 1 diabetes, insulin glulisine was non-inferior to insulin lispro (in both adult and paediatric patients) and to RHI (in adult patients). In adult patients with type 2 diabetes, insulin glulisine was non-inferior (and superior in one study) to RHI and (with basal insulin glargine) more effective than premixed insulin.

Insulin degludec (IDeg)
It is a new generation ultra-long-acting basal insulin acting >24 hrs. The ultra-long effect of IDeg is primarily a result of the slow release of IDeg monomers from soluble multihexamers that form after subcutaneous injection, resulting in a long half-life and a smooth and stable pharmacokinetic profile at steady state. These attributes are expected to provide improved glycemic control and to lower the risk of hypoglycemia, relative to currently available basal insulin analogs.

In a large 16-week, randomized, open-label, parallel-
A recent study indicates that pramlintide with each meal lowered the markers of oxidative stress along with the post-meal glucoses. Another study showed that pramlintide plus basal insulin was as effective as basal/bolus insulin in controlling T2DM with an additional advantage of significant weight loss in patients treated with pramlintide. Hypoglycaemia can occur particularly in the first 4 weeks of treatment. Decreasing the dose of pre-meal insulin by 50% when starting therapy avoids this problem. Pramlintide also causes some weight loss, reduces HbA1c by 0.3–0.6%, and significantly lowers postprandial glucose.

The main side effect of pramlintide is bloating, nausea, and vomiting. It is therefore started slowly—at 60 μg before meals inT2DM. Patients on pramlintide and insulin are at a higher risk of hypoglycaemia and should be instructed accordingly.

The role of pramlintide in the treatment of type 2 DM is unclear but it may be of some benefit to those patients already on insulin regimens.

5. Dopamine D2-receptor agonists

Bromocriptine is an ergot alkaloid dopamine-D2-receptor agonist that has been available since 1978 to treat patients with prolactinomas and Parkinson’s disease. Although bromocriptine quick release has only been licensed since 2010 by the US Food and Drug Administration (FDA) for the treatment of type 2 diabetes as an adjunct to lifestyle changes, its effects on glycaemic variables have been noted since 1980. Bromocriptine produces its effects without increasing insulin concentrations, possibly by altering the activity of hypothalamic neurons to reduce hepatic gluconeogenesis through a vagally mediated route. In a randomised trial of 3095 patients, bromocriptine quick release (as monotherapy or in combination with two blood-glucose-lowering drugs, including insulin) reduced the risk of cardiovascular disease compared with placebo (hazard ratio 0.60, 95% CI 0.35–0.96) by 52 weeks.

6. Sodium–glucose-cotransporter-2 (SGLT2) inhibitors

The kidneys contribute to glucose homoeostasis through gluconeogenesis, glucose use, and glucose reabsorption from the glomerular filtrate. Renal gluconeogenesis might contribute 20–25% of total glucose production in the fasting state, most of which can be used immediately by the kidney. About 180 L of plasma is normally filtered daily through the kidneys, and represents about 180 g of glucose if the average plasma glucose concentration is 5.5 mmol/L. All of this glucose is normally reabsorbed, mostly through SGLT2, a low-affinity high-capacity transporter, located predominantly in the brush border membrane of the S1 segment of the proximal tubule.

In type 2 diabetes, renal gluconeogenesis is increased and renal glucose reabsorption might be enhanced because of up regulation of the SGLT2 transport. Although hyperglycaemia often exceeds the renal threshold in type 2 diabetes, inhibition of SGLT2 can increase the glucosuria sufficiently to reduce hyperglycaemia. Several SGLT2 inhibitors are undergoing development, including dapagliflozin, canagliflozin, ASP1941, LX4211, and BI10773.

Dapagliflozin reduces fasting and postprandial plasma concentrations of glucose and HbA1c and bodyweight with low risk of hypoglycaemia. It can be used alone.
or in combination with established glucose lowering drugs, including insulin.\textsuperscript{68,69} This inhibitor was similarly effective in reducing HbA1c concentrations in patients with drug-naive and insulin-treated diabetes; the effect on weight loss, however, was often more striking in patients with longer duration of diabetes.\textsuperscript{70} Dapagliflozin was associated with increased risk of genital and urinary tract infections in most studies.\textsuperscript{71,72} but these were typically mild and managed with standard intervention.

7. 11β-hydroxysteroid-dehydrogenase-1 inhibitors

11β-hydroxysteroid dehydrogenase 1 predominantly converts low-activity cortisone to the more active cortisol. 11β-hydroxysteroid dehydrogenase 2 converts cortisol to cortisone. It is mainly expressed in tissues that also express the mineralocorticoid receptor (especially the kidneys), allowing aldosterone to bind to this receptor.\textsuperscript{6} The phenotypic and metabolic similarities between metabolic syndrome and Cushing's syndrome have sparked interest in the therapeutic potential of inhibiting 11β-hydroxysteroid dehydrogenase 1 to reduce cortisol formation in the liver and adipose tissue.\textsuperscript{73}

INCBI13739 (200 mg) an 11β-hydroxysteroid dehydrogenase 1 inhibitor, added on to metformin in patients with type 2 diabetes for 12 weeks reduced HbA1c by 0.6%, fasting plasma glucose concentrations by 1.33 mmol/L, and homoeostasis model assessment– insulin resistance by 24% compared with placebo. Reductions were also noted in concentrations of total cholesterol, LDL cholesterol, and triglycerides in patients with hyperlipidaemia, offering possible additional cardiovascular benefits.\textsuperscript{74}

8. Dual PPAR (α + γ) agonist

PPAR-γ agonists (e.g., pioglitazone) improve insulin sensitivity and are an established treatment for type 2 diabetes, whereas PPAR-α agonists (fibrates) are for dyslipidaemia, particularly high triglyceride and low HDL concentrations. The effects of PPAR-γ and PPAR-α agonists are fully retained when used together. Thus, dual PPAR-α and PPAR-γ agonists (glitazars) were developed to achieve a combined effect on lipids and glucose. Development of previous dual agonists, such as tesaglitazar and muraglitazar, was stopped because of adverse events, but aleglitazar (a newer dual PPAR-α and PPAR-γ agonism) seems to have a better side-effect profile.\textsuperscript{75} Administration of aleglitazar (300–900 μg once a day for 6 weeks) to patients with type 2 diabetes resulted in dose-dependent improvements in fasting and postprandial glucose concentrations, reduced insulin resistance, and improved lipid variables.\textsuperscript{112} In a 16-week study, patients with type 2 diabetes were randomly assigned to aleglitazar (50–600 μg) or placebo, or to open label pioglitazone 45 mg once a day. Aleglitazar reduced HbA1c in a dose-dependent manner (from –0.36%, 95% CI 0 to –0.70, p=0.048, with 50 μg to –1.35%, –0.99 to –1.70, p<0.0001, with 600 μg). The typical side effects of PPAR-γ agonism, oedema and weight gain, were less severe with doses that were smaller than 300 μg aleglitazar than with pioglitazone.\textsuperscript{76} The effects of aleglitazar on the incidence of cardiovascular disease and mortality in patients with type 2 diabetes after a recent acute coronary syndrome are being assessed in a phase 3 trial (ALECARDIO).\textsuperscript{77}

9. Glucokinase activator

The phosphorylation of glucose by glucokinase after entry into the β cell affects the rate of glucose metabolism and subsequent ATP production, which closes potassium–ATP channels and initiates insulin secretion.\textsuperscript{78} To enhance glucokinase action in β cells, several glucokinase activators have been developed, including piragliatin, compound 14, R1511, AZD1656, AZD6370, compound 6, and ID1101.\textsuperscript{79} Glucokinase activators increased insulin concentrations and reduced glucose concentrations in animal models of diabetes and patients with type 2 diabetes.\textsuperscript{80} Glucokinase activators can additionally reduce glucose concentrations through effects on hepatic glucose metabolism. Glucokinase activation is associated with increased concentrations of triglycerides and risk of hypoglycaemia.\textsuperscript{81}

10. Bile acid sequestrants

Bile acid sequestrants are well established for the treatment of dyslipidaemia, and reduce the risk of cardiovascular disease. They also reduce glucose concentrations in patients with type 2 diabetes.\textsuperscript{82} The mechanism of action is not known, but is possibly mediated by activation of liver farnesoid receptors. In 2009, the FDA licensed colesevelam to improve glycaemic control in patients with type 2 diabetes as an adjunct to lifestyle changes. Colesevelam reduced HbA1c concentrations by 0.50–0.54% when used in combination with metformin, sulphonylureas, or insulin, without increasing the risk of hypoglycaemia.

11. GIP antagonists

GIP, like GLP-1, potentiates glucose-dependent insulin secretion, but unlike GLP-1, it promotes fat deposition in the adipocytes, does not inhibit glucagon secretion, and has little effect on food intake, satiety, gastric emptying, or bodyweight.\textsuperscript{53} Studies of animal models of diabetes have shown that blocking GIP action increases energy expenditure, and reduces fat deposition and lipotoxicity. This inhibition has a favourable effect on glucose homoeostasis, enhancing muscle glucose uptake,
reducing hepatic glucose output, and improving β-cell function." Hence, GIP-receptor antagonists are potential treatments for patients with type 2 diabetes. Orally active insulin releasing GIP agonists have also been reported.84

12. Metabolic surgery

In 1995, Pories and colleagues described the outcomes of 608 patients who underwent gastric bypass over 14 years and noted that weight control was durable. 83% (121 of 146) of patients with type 2 diabetes maintained normal concentrations of HbA1c and plasma glucose.85 The benefits of bariatric surgery seem to exceed those attributable entirely to weight loss, hence the term metabolic surgery is favoured rather than bariatric surgery. The several types of metabolic surgery include gastroplasty, laparoscopic adjustable gastric banding, sleeve gastrectomy, gastric bypass, and biliopancreatic diversion.86 The results of a meta-analysis of 621 studies with 135 246 patients showed that overall 78.1% of patients with diabetes had resolution, and an additional 8.5% showed improved glycaemic control, with the greatest weight loss and resolution of diabetes in patients who underwent biliopancreatic diversion, followed by gastric bypass, and then laparoscopic adjustable gastric banding.87 Thus the question of whether metabolic surgery could be used as a primary mode of treatment for type 2 diabetes was asked. In a randomised controlled trial, rates of remission of type 2 diabetes (defined as fasting glucose ≤7 mmol/L and HbA1c <6.2% without glycaemic treatment) were higher in the patients with type 2 diabetes for less than 2 years and noted that weight control was durable. 83% (121 of 146) of patients with type 2 diabetes maintained normal concentrations of HbA1c and plasma glucose.85 Hence, GIP-receptor antagonists are potential treatments for patients with type 2 diabetes.

Rapid remission of type 2 diabetes after gastric bypass and biliopancreatic diversion is independent of the amount of weight loss. The mechanisms resulting in weight loss and diabetes remission after surgery are multifactorial, but gut hormones might play an important part.88,89 Gastric bypass surgery increases postprandial GLP-1 and peptide YY concentrations, and reduces basal ghrelin concentrations;81 these changes lead to weight loss and improve β-cell function. In studies of animals, gastric bypass prevented the reduction in energy expenditure that is usually noted with medical weight loss. Moreover, diet-induced thermogenesis increased compared with bodyweight-matched controls.

SELF-MONITORING OF BLOOD GLUCOSE

Self-monitoring of blood glucose (SMBG) is widely recognized as a core component of effective diabetic self-management in patients with insulin DM.91 Most evidence indicates that SMBG contributes to good glycemic control among type 192 and type 2 diabetic93 patients. The role of SMBG is more controversial in patients of T2DM who are treated with OGAs.

In a cost effectiveness analysis of a UK clinical trial, 453 patients with non-insulin treated type 2 diabetes were divided into Standardized usual care (control) compared with additional self monitoring of blood glucose with/without training in self interpretation of the results. It was observed that Self monitoring of blood glucose with or without additional training in incorporating the results into self care was associated with higher costs and lower quality of life in patients with non-insulin treated type 2 diabetes.94

ESMON trial was done to assess the effect of self monitoring of blood glucose concentrations on glycaemic control and psychological indices in patients with newly diagnosed type 2 diabetes mellitus. 184 people aged <70 with newly diagnosed type 2 diabetes were randomized to SMBG (n=96) or conventional treatment (n=88) for one year with follow-up at three monthly intervals. There were no significant differences between groups at any time point (12 months) in HbA1c (6.9 (0.8)% v 6.9 (1.2)%, P=0.69), BMI (33.1 (6.4) v 31.8 (6.0) P=0.32), use of oral hypoglycaemic drugs, or reported incidence of hypoglycaemia.95 The following are ADA 2011 Guidelines recommendation for SMBG.96

- SMBG should be carried out three or more times daily for patients using multiple insulin injections or insulin pump therapy.
- Continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens can be a useful tool to lower A1C in selected adults (age>25 years) with type 1 diabetes.
- For patients using less-frequent insulin injections, non-insulin therapies, or medical nutrition therapy (MNT) alone, SMBG may be useful as a guide to the success of therapy.
- When prescribing SMBG, ensure that patients receive initial instruction in, and routine follow-up evaluation of, SMBG technique and their ability to use data to adjust therapy.

PREVENTION OF T2DM

It is now clear through 3 landmark studies that Lifestyle Management (LSM) is effective in reducing the conversion of high-risk subjects with IGT to T2DM.97-98 The Diabetes Prevention Program Research Group have shown that intensive lifestyle interventions that encourage people to achieve and maintain weight-loss are effective in lowering the incidence of T2DM.99 In the Finnish Diabetes Prevention
Intensive glycaemic control has been suggested as an effective approach to reduce the burden of cardiovascular disease and microvascular complications in people with diabetes. Current guidelines recommend a target glycated haemoglobin (HbA1c) level of 7% or less. The results of major randomised controlled trials on the benefits of such treatment are, however, controversial.

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study an intensive glucose lowering regimen was associated with increased mortality (hazard ratio 1.22, 95% confidence interval 1.01 to 1.46, P=0.04). A statistically significant reduction in the rate of microvascular and renal events after intensive glycaemic control was reported in the United Kingdom Prospective Diabetes Study (UKPDS) 33 on intensive blood glucose control with metformin compared with conventional treatment and risk of complications in patients with type 2 diabetes and the Action in Diabetes and Vascular disease: preterAx and diamicron MR Controlled Evaluation (ADVANCE) trial, whereas in the Veterans Affairs Diabetes Trial (VADT) microvascular complications were the same in both the intensive therapy and the control groups.

In a meta-analysis of data from 13 randomized controlled trials (including 34 533 patients, 18 315 received intensive glucose lowering treatment and 16 218 standard treatment) Intensive treatment showed no benefit of intensive glucose lowering treatment on all cause mortality or death from cardiovascular causes in adults with type 2 diabetes. Furthermore, a 19% increase in all cause mortality and a 43% increase in death from cardiovascular causes cannot be ruled out. This suggests that over a treatment period of five years, 117 to 150 patients would need to be treated to avoid one myocardial infarction and 32 to 142 patients would avoid one episode of microalbuminuria, whereas one severe episode of hypoglycaemia would occur for every 15 to 52 patients. Thus current evidence does not justify strict glycemic control in all patients of T2DM.

### CARDIOVASCULAR RISK ESTIMATES IN TYPE 2 DIABETES

Accurate cardiovascular disease (CVD) risk estimates can inform choice of therapeutic strategies for individuals, provided they have been appropriately validated. Risk calculators are of particular relevance in diabetic patients given their 2–4 times higher CVD risk compared with the nondiabetic population. Framingham Study risk equations for coronary heart disease (CHD) and CVD and the Systematic Coronary Risk Evaluation (SCORE) Project risk scores for fatal CHD and CVD, have been validated prospectively in general populations but not in diabetic subjects. Table 3 shows various scores developed for CV risk estimation and factors used in Individual score.

**Table 3: CVD/CHD risk scores primarily developed in individuals with diabetes**

<table>
<thead>
<tr>
<th>Name of risk score</th>
<th>Risk factors included in score</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS risk engine (UKPDS 56)</td>
<td>Age at diagnosis of DM, sex, ethnicity, smoking, HbA1c, systolic BP, total-cholesterol : HDL-cholesterol ratio, duration of DM</td>
</tr>
<tr>
<td>Oxford risk engine (UKPDS risk engine version 3)</td>
<td>Age at diagnosis of DM, sex, ethnicity, smoking, HbA1c, systolic BP, total cholesterol : HDL-cholesterol ratio, duration of DM</td>
</tr>
<tr>
<td>Diabetes Audit and Research in Tayside, Scotland (DARTS)</td>
<td>Age at diagnosis of DM, sex, systolic BP, duration of DM, smoking, total cholesterol, HbA1c, treated hypertension, height</td>
</tr>
<tr>
<td>Swedish National Diabetes Register (NDR)</td>
<td>Age at diagnosis of DM, sex, smoking, duration of diabetes, BMI, systolic BP, HbA1c, antihypertensive drugs, lipid-lowering drugs</td>
</tr>
<tr>
<td>Atherosclerosis Risk in Communities (ARIC)</td>
<td>Age, ethnicity, smoking, systolic BP, use of antihypertensive medication, total cholesterol, HDL; alternative model includes: BMI, WHR, sport activity, Keys score for diet, serum creatinine, serum albumin, WBC, factor VIII, LVH, and IMT</td>
</tr>
<tr>
<td>Hong Kong Diabetes Registry (HND)</td>
<td>Age, sex, smoking, duration of diabetes, systolic BP, GFR, ACR, non-HDL-cholesterol</td>
</tr>
</tbody>
</table>

Study, a lifestyle intervention in middle-aged, overweight persons resulted in a 58% reduction or postponement of the overall incidence of diabetes. Furthermore, pharmacologic management with metformin prevented the conversion of IGT to T2DM in 31% compared with 58% for LSM. The cost-effectiveness of LSM for all ages has been established, but similar calculations suggest that use of metformin for patients older than 65 years is not cost-effective because of lack of efficacy in this age group. With 57 million prediabetic individuals, consisting of 23.9% of the population, whose annual rate of conversion from prediabetes to T2DM is about 10%, there is a strong rationale to prevent development of diabetes and its complications with an aggressive approach.

**IMPORTANT OF INTENSIVE GLYCAEMIC CONTROL**

Intensive glycaemic control has been suggested as an effective treatment to reduce the burden of cardiovascular disease and microvascular complications in people with diabetes. Current guidelines recommend a target glycated haemoglobin level (HbA1c) of 7% or less. The results of major randomised clinical trials on the benefits of such treatment are, however, controversial.

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