Treating Diabetes
Current strategies in the management of Type 2 diabetes

by Dr Stanley Liew

The explosion in the number of people affected with diabetes worldwide is staggering. Over 90% of all cases of diabetes are Type 2 diabetes. It is a heterogeneous group of metabolic defects which show itself in the form of hyperglycaemia. The real danger of diabetes is its devastating long-term complications, including cardiovascular disease, renal failure, blindness and limb loss.

It is widely acknowledged that current pharmacological treatments improve the morbidity and mortality of people with diabetes. Clinical studies have consistently demonstrated that early intervention and intensive glycaemic management can improve long-term diabetes outcomes.

Unfortunately, majority of patients with diabetes fail to achieve the glycaemic treatment goals established by expert consensus based on evidence-based clinical trials. The inability to attain glycaemic target goals is partly due to the lack of medications with durable efficacy and minimal side effects. Public health authorities have a vital role in helping patients with diabetes to improve their diabetes control.

Early Detection and Diagnosis of Diabetes
Type 2 diabetes has an asymptomatic pre-clinical phase which often goes undetected. Even in developed countries, a large proportion of people with diabetes are undiagnosed. Complications are commonly present at the time of diagnosis of Type 2 diabetes.1 There is some indirect evidence suggesting that early detection may be beneficial. In spite of the lack of direct evidence, early detection through screening is being tried out by many organisations in the world.

Screening strategies include risk assessment and measurement of blood glucose. Screening tests are followed by diagnostic tests. In 2011, the World Health Organization (WHO) adopted the use of HbA1c as a diagnostic test for diabetes.2

The WHO and American Diabetes Association now recommends the following options for diagnosing diabetes:
Fasting plasma glucose (FPG) ≥ 7.0 mmol/l (126 mg/dl)*

OR

75g Oral Glucose Tolerance Test with FPG ≥ 7.0 mmol/l (126 mg/dl) and/or 2-hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl)*

OR

HbA1c ≥ 6.5%*

OR

In the presence of classical diabetes symptoms, a random plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

*In asymptomatic individuals with a single abnormal test, the abnormal test should be repeated to confirm the diagnosis unless the result is unequivocally elevated.

Management of Type 2 Diabetes

Current strategies in the management of Type 2 diabetes should stress on the importance of diabetes prevention, screening high-risk individuals, lifestyle modifications in the pre-diabetes stage and intensive glycaemic control of Type 2 diabetes, especially the early years of disease. Public awareness of lifestyle modification can be raised. Most people with Type 2 diabetes would benefit from clear and simple practical advice on the healthy changes in diet and physical activity.

Recent studies have highlighted the potential risks of hypoglycaemia in intensive glycaemic control. Therefore, most guidelines have moved to the target HbA1c treatment goal of 7%.

Lifestyle modification can only achieve glycaemic control in a minority of people with diabetes, and then typically only for a limited period of time after diagnosis. Initiation of pharmacological agents is almost inevitable for most patients with Type 2 diabetes.

The natural history of Type 2 diabetes is the progressive failure of the pancreatic islet beta-cell. As a consequence, intensification of medications, either in dosage or in combination therapy, is required over time. Eventually, insulin will be the only viable glucose-lowering therapy which can maintain blood glucose control after a long duration of diabetes.

In the last two decades, the range of pharmacological agents available to treat hyperglycaemia has increased greatly. Nevertheless, the cost-effectiveness and long-term safety of the newer agents are yet to be established. Many algorithms and guidelines provide guidance on ways in which glucose-lowering agents can be initiated and used either alone or in combination.

Both treatment goals and use of pharmacological agents should be individualised, based on patient-specific considerations, namely current HbA1c, comorbidities, disease duration, biological age, availability of resources, and risks of hypoglycaemia.

Metformin

Most guidelines consider metformin as the first-line oral diabetes medication. Activation of AMP-kinase by metformin results in decrease of hepatic glucose production and modest increase of glucose transport in skeletal muscle. The overall effect is a decrease in hepatic gluconeogenesis due to improvement in hepatic insulin sensitivity. The unassailable position of metformin as a first drug of choice is due to its favourable effects on weight, low cost, and low hypoglycaemia risk. Nevertheless, the downside is its common gastrointestinal side effects and the contraindication in renal impairment. Lactic acidosis is rare and overplayed. The reported incidence
of lactate acidosis in patients with metformin is about three per 100,000 patient years, and some experts consider metformin as a “bystander” and not directly responsible for the lactic acidosis.

**Sulphonylureas**

Until recent years, sulphonylureas have been regarded as the second-line agents. Sulphonylureas act by binding to the SUR-1 sub-unit of KATP channels of pancreatic beta-cells, resulting in insulin release. They are potent, relatively cheap, and have fast onset of action. The undesirable properties are hypoglycaemia, weight gain, and potential lack of durability of efficacy.

Tolbutamide was first implicated with increased cardiovascular mortality in the University Group Diabetes Program study. The controversy on cardiovascular safety of sulphonylureas is unresolved. Plausible mechanisms have been related to blockage of SUR-2 receptor in myocardial cells and impaired ischaemic preconditioning of the heart. Newer sulphonylureas such as Gliclazide and Glimepiride are believed to have greater specificity on SUR receptors in pancreatic beta-cells.

**Dipeptidyl Peptidase-4 (DPP-4) Inhibitors**

DPP-4 inhibitors act to increase levels of endogenous incretin hormones. This enhancement of incretin effects results in increased insulin secretion, decreased postprandial glucagon levels, and lowered glucose levels.

The four currently available DPP-4 inhibitors – sitagliptin, vildagliptin, saxagliptin, and linagliptin – are highly selective DPP-4 inhibitors. They have proven efficacy when used as monotherapy, or combined with metformin and sulphonylurea. The main advantages of this class of drugs are its glucose-lowering effects without weight gain or significant hypoglycaemia.\(^3\)

As they are comparatively new, there is a lack of long-term efficacy and safety data. A few studies assessing its cardiovascular safety are ongoing. If these concerns and cost effectiveness are addressed, they could potentially become the drug of choice after metformin.

**Glucagon-Like Peptide Receptor Agonists (GLP-1 RA)**

GLP-1 RA such as liraglutide and exenatide are incretin mimetics given as subcutaneous injections. They have slightly greater HbA1C reductions compared to DPP-4 inhibitors. In addition to glycaemic effects, GLP-1 RA has beneficial effect on weight reduction. Similar to DPP-4 inhibitors, they have efficacious glucose lowering with minimal hypoglycaemia risk. Their main side effects are nausea and vomiting, which usually resolve within a few weeks. In rats and mice, exposure to GLP-1 RA has resulted in thyroid c-cell stimulation, but no evidence of such an effect has been seen in humans. At present, their use is mainly limited by cost.

**Pioglitazone**

Thiazolidinediones (peroxisome proliferator-activated receptor-gamma agonist) effectively lower blood glucose when used as mono-, dual- or triple-therapy. Pioglitazone is the only drug of this class still widely available.

Their side effects and safety concerns have limited their use in recent years. The most common adverse effects are weight gain and fluid retention which may result in peripheral oedema and congestive heart failure. Another concern is the increased incidence of fractures, especially in females. Some meta-analyses suggest an increased risk of myocardial infarction with rosiglitazone, although this was not apparent in the RECORD study. Pioglitazone has not been associated with an increase in cardiovascular risk, and the PROactive study reported some improved cardiovascular outcomes.\(^4\) The latest suggestion of a very small increased risk of bladder cancer with prolonged pioglitazone exposure is likely to further curtail its use.
Acarbose

Acarbose is an alpha-glucosidase inhibitor which has been popular before the introduction of the newer oral diabetes medications. It inhibits alpha-glucosidase required in the digestion of complex carbohydrates, thus slowing the intestinal absorption of carbohydrate in the form of glucose. It is effective in providing a modest decrease in glycaemic levels. Gastrointestinal side effects such as flatulence and diarrhoea are frequent.

Sodium Glucose Co-Transporters-2 (SGLT2) Inhibitors

SGLT2 inhibitors lower blood glucose by blocking SGLT2 which are present in early proximal tubule and responsible for 90% of renal glucose reabsorption. They work independently of insulin to prevent glucose re-absorption from the glomerular filtrate resulting in a reduced renal threshold for glucose, glycosuria and net calorie loss. They provide a novel insulin-independent approach for blood glucose lowering without causing hypoglycaemia. Studies suggested that they can be used as monotherapy or in combination with metformin or insulin. Treatment is associated with mean weight loss and a small reduction in blood pressure.5

Dapagliflozin and canagliflozin were approved in Europe and the United States, respectively, for the treatment of Type 2 diabetes. They are potent and highly selective SGLT2 inhibitors. Their main advantages are glucose lowering without significant risk of hypoglycaemia and the potential for weight loss. Vulvovaginitis and balanitis are the most common adverse effects.

Insulins

The options for insulin therapy have expanded considerably. Human insulin is slowly being replaced by insulin analogues in developed countries. The modern insulin analogues showed similar efficacy in glycaemic control, but the hypoglycaemia rates were lower compared to human insulin. The rapid insulin analogues are insulin aspart, glulisine and lispro, and the basal long acting insulin analogues are insulin glargine and detemir.

In most algorithms, the final step is to start insulin if combination or triple oral therapy has failed to achieve target glycaemic control. Intensified insulin therapy in Type 2 diabetes has been shown to improve metabolic control and improve clinical outcomes. The common side effects of insulin are hypoglycaemia and weight gain.

Conclusions

Lifestyle modification remains the cornerstone for the management of Type 2 diabetes throughout the course of the disease. Intensification of pharmacologic therapy is required to achieve target diabetes control without unacceptable risk of hypoglycaemia. Patients who are unable to successfully reach HbA1c goals on combination oral therapy should be considered for insulin therapy.

Table 1. Current Therapeutic Agents in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Examples of Medications</th>
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<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
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<tr>
<td>Sulphonylureas</td>
<td>Gliclazide, Glimepiride, Glipizide, Glibenclamide</td>
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<tr>
<td>DPP4 inhibitors</td>
<td>Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin</td>
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<tr>
<td>GLP-1 receptor agonists</td>
<td>Liraglutide, Exenatide</td>
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<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone</td>
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<tr>
<td>Alpha-glucosidase</td>
<td>Acarbose</td>
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<tr>
<td>inhibitors</td>
<td>Dapagliflozin, Canagliflozin</td>
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<tr>
<td>SGLT2 inhibitors</td>
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<tr>
<td>Insulin</td>
<td>Rapid-acting: Aspart, Glulisine, Lispro.</td>
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<tr>
<td></td>
<td>Long-acting: Glargine, Detemir</td>
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The choice of pharmacological agents should be individualised, based on patient-specific considerations, including availability, prevailing HbA1c, comorbidities, disease duration, biological age, costs, and risks of hypoglycaemia. Patients can be encouraged to participate in the shared decision making with physicians in the selection of therapeutic options. This could lead to better patient adherence and improved diabetes control.6

References