Advances in the management of type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disorder caused by a combination of insulin resistance and β-cell dysfunction [1].

It is associated with an increased and premature risk of cardiovascular disease as well as specific microvascular complications such as retinopathy, nephropathy and neuropathy. Established macrovascular pathology is common at the time of diagnosis of T2DM, suggesting either latency in diagnosis and/or an atherogenic prediabetes [2,3] state.

The first-line treatment for T2DM is diet, weight control and physical activity. If the blood glucose level remains high despite these lifestyle modifications, usually, tablets are prescribed to reduce the blood glucose level.

Because of the progressive nature of T2DM, many individuals require insulin to optimize glycaemic control over time as oral hypoglycaemic agents fail to achieve targets. Data from the UK Prospective Diabetes Study (UKPDS) suggest that 53% of patients will require insulin 6 years following the diagnosis and 75% of patients will need multiple treatments after 9 years [4].

Although insulin treatment is very effective in achieving glycaemic control, its use is invariably associated with weight gain because of increased body fat mass, in particular, abdominal obesity [5,6]. Increased abdominal obesity in turn may lead to worsening of insulin resistance and therefore increasing insulin requirements, and a vicious circle may ensue. Along with weight gain, the use of insulin can also cause problems with episodes of hypoglycaemia if insulin treatment is not managed appropriately.

Medicines for type 2 diabetes mellitus (glucose-lowering tablets)

Several different types of medicine, usually taken as tablets, are used to treat T2DM. Patients may need to take a combination of two or more medicines to control the blood glucose level.

Medications that primarily stimulate insulin secretion

Sulphonylureas

Sulphonylureas increase the amount of insulin that is produced by the pancreas. Examples of sulphonylureas include the following:

(1) glibenclamide
(2) gliclazide
(3) glimerpirizide
(4) glipizide
(5) gliquidone.

They appear to have an effect similar to metformin, and they lower glycated haemoglobin (A1C) by ∼1.5 percentage points [7]. The major adverse side effect is hypoglycaemia, but severe episodes, characterized by the need for assistance, coma or seizure, are infrequent. However, such episodes are more frequent in the elderly. Episodes can be both prolonged and life threatening, although these are very rare. Several of the newer sulphonylureas have a relatively lower risk for hypoglycaemia [8]. In addition, a weight gain of ∼2 kg is common with the initiation of sulphonylurea therapy. This may have an adverse impact on the risk of cardiovascular diseases (CVD), although it has not been established.

Nateglinide and repaglinide

Nateglinide and repaglinide stimulate the release of insulin by the pancreas. They are not commonly used but may be an option if meals are consumed at irregular times. This is because their effects do not last very long, but they are effective when taken just before a meal.

Nateglinide and repaglinide can cause side effects, such as weight gain and hypoglycaemia (low blood glucose).

Medications that primarily lower glucose levels by their actions on the liver, muscle and adipose tissue

Metformin

Metformin is the only biguanide available in most countries. Its major effect is to decrease hepatic glucose output and reduce fasting glycaemia. Typically, metformin monotherapy will lower A1C by ∼1.5 percentage points [9,10]. It is generally well tolerated, with the most

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common adverse effects being gastrointestinal. Although always a cause for concern because of its potentially fatal outcome, lactic acidosis is quite rare (<1 case/100 000 treated patients) [11]. Metformin monotherapy is usually not accompanied by hypoglycaemia and has been used safely, without causing hypoglycaemia, in patients with prediabetic hyperglycaemia. The major nonglycaemic effect of metformin is either weight stability or moderate weight loss, in contrast to many of the other blood glucose-lowering medications. The UKPDS showed a beneficial effect of metformin therapy on CVD outcomes that needs to be confirmed.

Glitazones (thiazolidinediones)

Thiazolidinediones (TZDs or glitazones) are peroxisome proliferator-activated receptor γ modulators; they increase the sensitivity of muscle, fat and liver to endogenous and exogenous insulin (insulin sensitizers) [12]. The limited data on the blood glucose-lowering effect of TZDs when used as a monotherapy have shown a 0.5–1.4% decrease in A1C. The most common adverse effects with TZDs are weight gain and fluid retention. There is an increase in adiposity, largely subcutaneous, with the redistribution of fat from visceral deposits shown in some studies. The fluid retention usually manifests as peripheral oedema, although new or worsened heart failure can occur. TZDs either have a beneficial or a neutral effect on atherogenic lipid profiles, with pioglitazone having a more beneficial effect than rosiglitazone [13].

Rosiglitazone has been withdrawn from use because of the increased risk of cardiovascular disorders, including heart attack and heart failure.

Medications that affect absorption of glucose

α-Glucosidase inhibitors

α-Glucosidase inhibitors reduce the rate of digestion of polysaccharides in the proximal small intestine, primarily reducing the postprandial glucose levels without causing hypoglycaemia. They are less effective in lowering glycaemia than metformin or sulphonylureas, reducing A1C by 0.5–0.8 percentage points [14]. As carbohydrate is absorbed more distally, malabsorption and weight loss do not occur; however, increased delivery of carbohydrate to the colon commonly results in increased gas production and gastrointestinal symptoms. This side effect has led to the discontinuation of α-glucosidase inhibitors by 25–45% of participants in clinical trials [14,15]. One clinical trial examining acarbose as a means of preventing the development of diabetes in high-risk individuals with impaired glucose tolerance showed an unexpected reduction in severe CVD outcomes [15].

Incretins [16]

Gliptins (DPP-4 inhibitors)

Gliptins work by preventing the breakdown of a naturally occurring hormone called glucagon-like peptide 1 (GLP-1). GLP-1 helps the body produce insulin in response to high blood glucose levels, but is rapidly broken down. By preventing this breakdown, gliptins (sitagliptin and vildagliptin) act to prevent high blood glucose levels, but do not result in episodes of hypoglycaemia. Patients may be prescribed a gliptin if they unable to take sulphonylureas or glitazones. They are not associated with weight gain.

Glucagon-like peptide 1 agonists

GLP-1 7-37, a naturally occurring peptide produced by the L-cells of the small intestine, stimulates insulin secretion. It binds strongly to the GLP-1 receptor on the pancreatic β cell and potentiates glucose-mediated insulin secretion. Exenatide is a GLP-1 agonist, an injectable treatment that acts in a manner similar to the natural hormone GLP-1. It is injected twice a day and boosts insulin production when there are high blood glucose levels, reducing blood glucose without the risk of hypoglycaemic episodes. It also leads to moderate weight loss in many patients who take it. It is mainly used in patients on metformin plus sulphonylurea who are obese (with a BMI of 35 or above).

Another GLP-1 agonist called liraglutide has recently been launched in the UK. It is a once-daily injection. Similar to exenatide, it is mainly used in patients on metformin plus sulphonylurea who are obese, and in clinical trials, it has been shown to cause moderate weight loss.

Others

Amylin agonists (pramlintide)

Pramlintide is a synthetic analogue of the β-cell hormone amylin. Currently, pramlintide is approved for use in the USA only as adjunctive therapy with insulin.

Pramlintide is administered subcutaneously before meals and slows gastric emptying, inhibits glucagon production in a glucose-dependent manner and predominantly decreases postprandial glucose excursions [17]. In clinical studies, A1C has been decreased by 0.5–0.7 percentage points [18]. The major clinical side effects of this drug, which is injected before meals, are gastrointestinal in nature. Approximately 30% of treated participants in the clinical trials have developed nausea. Weight loss associated with this medication is ~1–1.5 kg over 6 months; as with exenatide, some of the weight loss may be the result of gastrointestinal side effects.

Rimonabant

Rimonabant is the first agent of the class of drugs that act on the novel endocannabinoid system (ECS). The ECS is a novel physiological neuroendocrine system that plays a key role in appetite and energy metabolism, both in the brain and in adipose tissue [19,20]. Animal studies have shown that blocking the ECS leads to weight loss and improved insulin sensitivity. Because of this effect, agents that block receptors (CB1 and CB2) in this system have been developed for the management of human obesity.

By blocking CB1 receptors, rimonabant has been shown to reduce weight by suppressing appetite and by modifying glucose and fat metabolism [21]. It is usually given at a dose of 20 mg once a day before breakfast. In

the brain, rimonabant reduces hunger and therefore results in weight loss, and in the adipose tissue, the drug increases the concentrations of adiponectin. This helps improve insulin sensitivity as reduced levels of adiponectin have been associated with increased insulin resistance. Because of this close link with various adipocytokines, agents within this group are hypothesized to play a role in atherogenesis and the pathophysiology of T2DM [22].

A1C of at least 7% should serve as a call to action to initiate or alter therapy with the goal of achieving an A1C level as close to the nondiabetic range as possible or, at a minimum, decreasing the A1C to less than 7%.

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Conflicts of interest

There are no conflicts of interest.

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