REVIEW ARTICLE

Type 2 Diabetes Mellitus: A Review of Pharmacological Treatment

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ABSTRACT

Background: *Type 2 diabetes mellitus, is a disease with a rising prevalence worldwide. It is currently estimated that 190 million people around the world suffer from diabetes mellitus, with over 330 million predicted to have the condition by 2025 and 366 million by the year 2030. It is predicted that the developing countries will contribute 77.6% of the total number of diabetic patients in the world by the year 2030. This rapidly growing prevalence among developing countries is attributed to the effects of urbanization, industrialization and globalization on these countries. There has been substantial progress over the last decade in the development of new agents for the treatment of type 2 diabetes especially focusing on the underlying pathophysiology. Despite this and the numerous guidelines from diabetes organisations only less than 40% of patients achieve recommended glycaemic targets. We therefore decided to do a review of the pharmacological treatment of type 2 diabetes mellitus to highlight the pharmacology and effectiveness of these agents and their roles in the management of type 2 diabetes.*

Methods: *We reviewed the literature on the subject using materials from library search, articles in journals, internet search and conference abstracts.*

Results: *The global burden of type 2 diabetes mellitus, the various pharmacological agents available for the treatment of type 2 diabetes mellitus, including novel agents were discussed.*

Conclusion: *The prevalence of type 2 diabetes mellitus is increasing worldwide and the predicted increase is much higher in developing countries compared to the developed countries. There are obviously an enormous number of therapies available for the treatment of type 2 diabetes mellitus and if effectively deployed it will be possible to achieve target diabetic control in most of our patients. This however, should not detract us from adopting measures that will reduce the prevalence of type 2 diabetes mellitus in our population bearing in mind that prevention is more cost effective especially given our low socioeconomic development and the very high predicted rise in the burden of type 2 diabetes mellitus in our developing world.*

KEYWORDS: Type 2 Diabetes mellitus; Pharmacological. treatment.

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INTRODUCTION

It is currently estimated that 190 million people around the world suffer from diabetes mellitus, with over 330 million predicted to have the condition by 2025[1] and 366 million by the year 2030[2]. An increase of as high as 146% is predicted to occur in developing countries, while the increase would only be about 47% in developed countries. This means that the developing countries will contribute 77.6% of the total number of diabetic patients in the world by the year 2030. This rapidly growing prevalence among developing countries is primarily as a result of the rapid demographic and epidemiological transitions occurring in these countries as a consequence of urbanization, industrialization and globalization[3,4].

As large as these prevalence figures are, they are thought to significantly underestimate the extent of the problem, since up to 50% of the population with diabetes are thought to remain undiagnosed and therefore untreated[5]. It is known that at the time of diagnosis 50% of these patients already have micro- and macrovascular complications which are known to adversely affect their quality of life and impose a heavy burden on health care systems[6-9]. The UKPDS provided evidence that tight glycaemic control can reduce the risk of complications[10]. Consequently glycaemic goals or targets have been set and various guidelines developed but despite the various guidelines only less than 40% of patients achieve target treatment goals[11,12] . Guidelines from American Diabetes Association (ADA), European Diabetes Policy Group, Canadian Diabetes Association (CDA), American Association of Clinical Endocrinologists, Latin American Diabetes Association and Asian-Pacific Type 2 Diabetes Policy Group, all recommend targets for HbA_{1C} less than 6-7% in patients with type 2 diabetes[13-18]. Fasting plasma glucose less than 6.0mmol/L is recommended where assessment of HbA_{1C} is not possible[19].

Type 2 diabetes is by far the most prevalent form of the disease, accounting for more than 90% of cases. It is a progressive disease that is characterized by continuous decline in beta-cell function in the presence of insulin resistance. On average patients have lost 50%

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of their beta-cell function by the time the diagnosis of diabetes is made[20] and about 80%-85% of type 2 diabetes patients are insulin resistant[21,22]. The UKPDS also reported that glycaemic deterioration is directly related to a progressive loss in beta-cell function, declining insulin secretion, and eventually beta-cell failure. This loss of beta-cell function was associated with whether patients failed monotherapy or combination therapy with oral secretagogues[23]. The addition of insulin therapy when maximal sulphonylurea therapy is inadequate can significantly improve glycaemic control without resulting in increased hypoglycaemia or weight gain[24]. It has long been established that intensive glucose control, including the use of insulin, is the best means available to prevent complications of type 2 diabetes. It is now clear that most patients with type 2 diabetes will require insulin in addition to oral agents to achieve the best outcomes of treatrment[25].

Given the significant public health burden of type 2 diabetes mellitus amongst adults and now increasingly among children, preventive measures need to be emphasized. According to the report of the Diabetes Prevention Program Study, a lifestyle intervention consisting of 150 minutes of exercise per week and a 7% weight loss over 2.8 years reduced the incidence of type 2 diabetes mellitus by 58% compared to placebo[26]. A number of pharmacological agents, in particular metformin, thiazolidinediones, Angiotensin Converting Enzyme inhibitors and orlistat, a gastrointestinal lipase inhibitor are all effective in delaying and perhaps preventing the onset of type 2 diabetes mellitus[27-30].

This review will be limited to the pharmacological aspect of treatment which is a very important and dynamic component of diabetic management. It includes discussions on the oral antidiabetic drugs and insulin, including newer therapies. Oral drugs for treatment of type 2 diabetes fall into three categories: (1) Drugs that primarily stimulate insulin secretion e.g. sulphonylureas, the meglitinide analogue, ripaglinide and the D-phenylalanine derivative nateglinide (2) Drugs that alter insulin action e.g metformin, and the thiazolidinediones (3) Drugs that principally affect absorption of glucose e.g acerbose and miglitol.

Sulphonylureas

These agents which include tolbutamide, chlorpropamide, tolazamide acetohexamide (first generation) and glyburide, glipide, gliclazide and glimepiride (second generation), cause hypoglycaemia by stimulating release of insulin from pancreatic beta-cells. Their effects in the treatment of diabetes are however more complex. Acute administration of these agents to type 2 diabetes patients increases insulin release from the pancreas reduces the hepatic clearance of the hormone and decreases serum glucagons levels[31]. With chronic administration, circulating levels decline and this is attributed to down-regulation of cell surface receptors for sulphonylureas on the pancreatic beta-cells. Sulphonylureas bind to sulphonylurea receptors and block the ATP-sensitive K^+ channel[32,33]. They thus resemble physiological secretagogues (e.g. glucose, leucine), which also lower the conductance of this channel. Reduced K^+ conductance causes membrane depolarization and influx of Ca^{2+} through voltage-sensitive Ca^{2+} channels.
Between 50% and 80% of properly selected patients will respond initially to a sulphonylurea agent. All the drugs appear to be equally efficacious. In all patients, continued dietary restrictions are essential to maximize the efficacy of sulphonylureas. Contraindications to the use of these drugs include type 1 diabetes mellitus, pregnancy, lactation, and for older preparations, significant hepatic or renal insufficiency[31].

Repaglinide

This drug like the sulphonylureas, stimulates insulin release by closing ATP-dependent potassium channels in pancreatic beta cells. It has short half-life of about 1 hour, allowing for multiple prepandial administration. It is metabolized primarily by the liver to inactive products. A small proportion (about 10%) is metabolized by the kidney. As with sulphonylureas, the major side effect is hypoglycaemia.

Nateglinide

This drug acts like the sulphonylureas and repaglinide by blocking ATP-sensitive potassium channels in pancreatic beta cells. It promotes a more rapid but less sustained secretion of insulin than do other available oral antidiabetic agents[34]. Its major therapeutic effect is reducing postprandial glycaemic elevations in type 2 diabetes mellitus patients[31].

Metformin

This agent does not cause hypoglycaemia and does not cause insulin release from the pancreas. It reduces glucose levels primarily by decreasing hepatic glucose production and by increasing insulin action in muscle and fat. At a molecular level, these actions are mediated at least in part by activation of the cellular kinase AMP-activated protein kinase (AMP kinase)[35,36]. Metformin reduces gluconeogenesis and reduces the

absorption of glucose from the intestine.

Acute side effect of metformin, which occur in up to 20% of patients include diarrhoea, abdominal discomfort, nausea, metallic taste, and anorexia. Intestinal absorption of vitamin B_{12} and folate is often decreased during chronic metformin therapy, and calcium supplements reverse effects of metformin on vitamin B_{12} absorption[31].

Metformin is the only therapeutic agent that has been demonstrated to reduce macrovascular events in type 2 diabetes[37]. Metformin can be administered in combination with sulfonylureas, thiazolidinediones, and/or insulin.

Thiazolidinediones

Troglitazone, the first of these agents to be introduced, has been withdrawn because it was associated with severe hepatic toxicity. Rosiglitazone and pioglitazone, the other examples, can lower haemoglobin A_{1C} levels by 1% to 1.5% in type 2 diabetes mellitus.

The thiazolidinediones are selective agonists for nuclear perixisome proliferator-activated receptor-(PPAR). PPAR activates insulin-responsive genes that regulate carbohydrate and lipid metabolism. Thiazolidinediones (Tzds) require insulin to be present for their action and exert their principal actions by increasing sensitivity in peripheral tissues and by lowering glucose production by the liver. They increase glucose transport into muscle and adipose tissue by enhancing the synthesis and translocation of specific forms of glucose transporters. They can also activate genes that regulate fatty acid metabolism in peripheral tissue. PPAR is thought to activate adipocyte hormones and/or adipokines, including adiponectin. Adiponectin is associated with increased insulin sensitivity and is reported to increase insulin sensitivity by elevating AMP kinase, which stimulates glucose transport into muscle and increases fatty acid oxidation[38]. Because AMP kinase is a common endpoint of both metformin and thiazolidinedione action, it has emerged as an attractive target for drug development[39]. PPAR agonists, such as the thiazolidinediones now generally known to improve glucose control (largely by improving insulin action in the periphery) and may improve a number of CVD risk factors, including hypertension, dyslipidaemia, and the vascular, haemodynamic, and haemostatic abnormalities that are common in those with diabetes[40].

Liver toxicity is much less with rosiglitazone and pioglitazone because they lack the tocopherol side chain that was included in the troglitazone molecule. These drugs have been reported to cause anaemia, weight gain, edema, and plasma volume expansion. Edema is particularly likely to occur when these drugs are combined with insulin.

There is a new class of compounds called the dual PPAR activators or "glitazars" and include muraglitazar and tesaglitazar. These agents exert their therapeutic effects by activation of both PPAR receptors (similar to the action of thiazolidinediones) and PPAR receptors (the receptor targeted by fibrates)[41]. These compounds offer the promise of a multitude of both glycaemic and lipid effects, with the hope that such therapy could be used in those with type 2 diabetes and dyslipidaemia to improve both glucose control and lipid measures (particularly HDL-C and triglycerides).

Glucosidase Inhibitors

These drugs reduce intestinal absorption of starch, dextrin, and disaccharides by inhibiting the action of -glucosidase in the intestinal brush border. They thus, diminish the absorption of carbohydrates with a consequent blunting of postprandial rise in plasma glucose in both normal and diabetic subjects[31]. Although these agents may be considered as monotherapy in elderly patients with predominantly postprandial hyperglycaemia, they are typically used in combination with other oral antidiabetic agents and/or insulin. -Glucosidase inhbibitors cause a dose-related malabsorption, flatulence, diarrhoea, and abdominal bloating.

Insulin

The discovery of insulin is attributed to Fredrick Banting, a young Canadian surgeon and Charles Best, a fourth-year medical student, in 1922[31]. The first product administered to patients was a less-than-pure product with highly variable interpatient and intrapatient effects. Zinc crystallization was the first method employed to extend the action of insulin, followed neutral protamine Hagedorn (NPH) and lente insulin as basal insulin alternatives. By the 1970s, purified animal insulins were available, followed in the 1980s by the development of recombinant human insulin. The rapid-acting insulin analogs (insulin lispro), were introduced into clinical practice in the 1990s. "Innovations in insulin therapy were clearly needed in terms of greater purity, less immunogenicity, and more predictability in lowering blood glucose (both basal and prandial glucose levels), to be as much as possible like the beta cell itself"[42].

Analogs of human insulin have been designed in recent years to better replicate physiologic insulin secretion by

the beta-cell. These preparations, by reducing interpatient and intrapatient variability in the pharmacokinetics are better able to provide glycaemic control with less risk of hypoglycaemic events[42].

Rapid-acting insulin analogs (insulin aspart, glulinase, and lispro) have a shorter duration of action compared with regular human insulin. They provide a short, rapid increase in plasma insulin secretion to respond to meal-stimulated glucose excursions. More importantly, patients do not have to take insulin injections 30 minutes before a meal but instead take their insulin at meal time, which is infinitely more convenient[43].

The introduction of insulin glargine expanded therapeutic alternatives of type 2 diabetes by providing a relatively peakless insulin that lasts almost 24 hours. Insulin detemir recently approved for use in the Unites States is associated with a consistent pharmacokinetic profile across patient age groups[44], with less intrapatient variability than either NPH insulin or insulin glargine[45,46] and apparently less weight gain[42].

In addition to these available forms of insulin, substantial body of research suggests that a variety of forms of inhaled insulin, as well as several orally administered products currently under intense study, have potential in the treatment of persons with type 1 and type 2 diabetes[47-52].

Why and when to Start Insulin in Type 2 Diabetes

Timely initiation of insulin optimizes blood glucose and improves prognosis. The UKPDS and other studies, which all used conventional human insulin products, achieved HbA_{1C} levels of 7%[37]. When these levels are achieved, there were average reductions of 20% to 30% of diabetic complications for every 1% reduction in HbA1c level. HBA_{1C} levels consistently > 7% indicate that a patient may benefit from insulin.

After oral antidiabetic drug (OAD) failure, combination insulin and OAD can improve glycaemic control with less weight gain than insulin alone. Some patients may benefit from insulin therapy as soon as dietary control becomes inadequate[53].

"Elevated fasting glucose levels indicate the need for basal insulin to suppress gluconeogenesis overnight. Elevated postmeal glucose levels indicate a need for bolus insulin to cover meal-related carbohydrate intake. Premixed insulin analog contains both rapid-acting and long-acting insulin, providing both background (basal) and mealtime (bolus) insulin"[53]. The Treat-to Target study[54] evaluated the use of the basal insulin analog glargine against NPH and found that target HbA1c levels of </=7% were achieved by 58% of patients receiving insulin glargine and by 57% of patients receiving NPH insulin. The difference between the two treatments was in the proportion of patients who experienced hypoglycaemia and this was greater in patients who received NPH insulin, especially during the overnight hours[54]. A significant quality of the anlog insulins is their very small likelihood to induce hypoglycaemia and their reproducible pharmacodynamics[53]. The diasadvantage of using basal insulin analogs alone is that mealtime glucose excursions are not covered. It has been reported[55] that people using conventional insulin regimens had much higher complication rates for the same HbA_{1C} level than the intensively managed patients who took preprandial insulin with every meal.

"Successful control ultimately depends on targeting both fasting and prandial glucose levels. Insulin should be considered early in the disease process before glycaemia reaches unacceptable levels, because this is when the greatest opportunity exists to prevent glucose toxicity and its eventual complications"[53].

Role of Incretins in the Treatment of Diabetes

It was long reported that sugar is more effective in provoking insulin secretion when taken orally than when administered intravenously[56,57]. It was subsequently discovered that two hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1, that are released from the upper and lower bowel augment glucose-dependent insulin release[58]. These hormones are called incretins and differentially stimulate insulin secretion. GIP has little effect on augmenting insulin secretion in type 2 diabetes, whereas GLP-1 significantly augments glucose-dependent insulin-secretion and is unsurprisingly an attractive target for therapeutic development in type 2 diabetes[31]. GLP-1 also reduces glucagon secretion, slows gastric emptying, and decreases appetite. It may thus have unique properties to reduce postprandial glucose excursions (i.e. increase in insulin, reduction of glucagons, slowing of gastric emptying) and also to induce weight loss[31].

Mechanism of Action of Incretins

The mechanisms by which incretins elicit their actions at the level of the beta cell are not well understood. Holz[59] reported a cAMP-dependent pathway for GLP-1R-mediated insulin secretion that works independently of protein kinase A (PKA) through the activation of a cAMP-regulated guanine nucleotide

exchange factor (cAMP-GEF) called exchange protein directly activated by cAMP (Epac). Epac stimulates calcium influx into a beta cell, potentiating calcium release from intracellular stores and triggering insulin granule exocytosis.

In addition, GLP-1 has been shown to increase levels of PKA in rodent islets, which may also be involved in its cytoprotective effects[60]. It was also reported that short-term GLP-1 treatment increased the transcription of genes that is involved in the control of cell growth and the regulation of cell-cycle transition, whereas longer treatment with GLP-1 increased the levels of genes regulating cell survival[60].

The mechanisms by which incretin hormones elicit cytoprotective effects on the beta cell is particular interest, because preservation and restoration of beta cell mass may contribute to the therapeutic potential of the incretins for the treatment of both type 1 and type 2 diabetes. Endoplasmic reticulum (ER) stress within the beta cell, possibly occurring as the result of the overproduction or misfolding of insulin, may be a contributing factor to increased beta cell apoptosis and loss of islet mass observed within diabetic patients and GLP-1 has been shown to modulate the ER stress pathway[61-65]. This may provide an explanation for the effects of GLP-1 on enhancement of insulin biosynthesis and beta cell survival under conditions of physiologic stress.

GLP-1 is rapidly inactivated (1-2 minutes) by the dipeptidyl peptidase IV enzyme (DPP-IV). Thus GLP-1 must be infused continuously to have therapeutic benefits. To overcome this research has been focused on developing GLP-1 receptor agonists that are resistant to DPP-IV but maintain the physiologic effects of the native incretin. Two of such drugs exendin-4 and NN2211 are currently undergoing clinical trials.

An alternative approach to elongating the activity of GLP-1 is to inactivate the DPP-IV protease, thereby increasing endogenous circulating GLP-1 levels. There are now a number of orally effective DPP-IV inhibitors undergoing clinical trials as well.

Exenatide (synthetic exendin-4) was initially discovered in 1992 during a search for a substance similar to exendin-3, which is found in the venom of a lizard species, Heloderma horridum[66]. Exenatide is isolated from the salivary secretions of heloderma suspectum, or the gila monster and is the first example of an endocrine hormone that is secreted from the salivary glands. Exenatide and GLP-1 share 53% of their amino acid sequences, although exanatide is neither an analog nor made from a structural alteration of GLP-1[67]. Exenatide is resistant to metabolism by DPP-IV and thus exerts a longer hypoglycaemic effect than does GLP-1.

The drug is indicated as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulphonylurea or both but who have not achieved adequate glycaemic control[66]. The terminal half-life of the drug is about 2.4 hours, with a bioavailability after subcutaneous injection of between 65 and 75%. It is eliminated predominantly by glomerular filtration followed by proteolytic degradation[66]. Clinical trials indicate that exenatide following twice daily subcutaneous administration (5g within one hour before morning and evening meals), significantly reduced HbA_{1C} levels, when maximim doses of a sulphonylurea, metformin, or both were ineffective[66]. The most common adverse effects are nausea, vomiting, diarrhoea, jitteriness, dizziness, headache, and dyspepsia. Drug-drug interactions with digoxin, lovastatin, lisinopril, and acetaminophen have been reported[66].

CONCLUSION

There are obviously an enormous number of therapies available for the treatment of type 2 diabetes mellitus, though some of these may not be readily available in our environment while others are still at developmental stages. These drugs if effectively deployed are capable of bringing about achievement of target diabetic control in our patients. This however, should not detract us from putting in place or adopting measures that will possibly reduce the prevalence of type 2 diabetes mellitus in our population bearing in mind that prevention is more cost effective especially given our low socioeconomic development and the very high predicted rise in the burden of type 2 diabetes mellitus in our developing world.

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