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Review Article

Pharmacological Therapy of Type 2 Diabetes Mellitus: New Perspectives

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Abstract

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. DM is classified into 2 main types according to whether the patient is insulin dependent (Type I) or non-insulin dependent (Type 2). Type 2 DM is the most common form, accounting for about 90 - 95% of cases with diabetes. Treatment of type I DM mainly depends on insulin. Treatment of type 2 DM usually necessitates a combination of changes in lifestyle and pharmacological treatment is necessary. This review sheds light on the benefits and limitations of different drugs, both current and future, for the treatment of type 2 DM with a special emphasis on the agents introduced within the last few years.

Keywords: *Insulin; Type 2; Diabetes; Management; Drugs*

Introduction

Type 2 diabetes mellitus (DM) usually results from insulin resistance with relative insulin deficiency or may be an insulin secretory defect with insulin resistance. This form of diabetes accounts for about 90 - 95% of cases with diabetes worldwide. Patients with type 2 DM include those who have insulin resistance and usually have relative insulin deficiency [1]. At least initially, and often throughout their lifetime, these patients do not need insulin treatment to survive. Most patients with this type of DM are often obese as obesity itself is one of the predisposing factors of insulin resistance [2]. This type of DM frequently goes undiagnosed for many years because hyperglycemia develops gradually and is often not severe enough for the patient to notice any of the classic symptoms of DM. Most cases of type 2 DM usually present with polyuria, polydipsia, blurred vision, fatigue, weight loss, numbness and paraesthesias [1]. The long-term complications of type 2 DM are either microvascular or macrovascular complications. The microvascular complications include diabetic retinopathy, nephropathy and neuropathy. Macrovascular complications include ischemic heart disease, cerebrovascular disease, peripheral arterial disease, chronic heart failure and cardiomyopathy [3].

Treatment of type 2 DM mainly depend on administration of drugs that enhance insulin release such as sulphonylurea and increase insulin sensitivity such as metformin. Resistance to these traditional agents lead to the development of new drugs that act at the molecular levels to counteract insulin resistance [4]. The aim of this review was to shed light on the benefits and limitations of the different drugs, both current and future, for treatment of type 2 DM with a special emphasis on the agents introduced within the last few years.

The traditional lines of therapy of type 2 DM

Metformin

Metformin is the most common form of biguanides available in most of the world that lowers hyperglycemia by reducing hepatic glucose output and increasing insulin sensitivity. Metformin monotherapy often lowers HbA1c by about 1.5 percentage points and it is generally well tolerated, with the most common adverse effects being gastrointestinal disturbances [1]. Metformin monotherapy is usually euglycemic but when combined with other agents such as insulin or sulfonylureas, it may lead to hypoglycemic attacks. Lactic acidosis is another rarely reported adverse effect of metformin but it may have a potentially fatal outcome [5].

Sulfonylureas

Sulfonylureas can decrease blood glucose levels by enhancing insulin secretion and increasing insulin sensitivity. They appear similar to metformin in efficacy at lowering HbA1c levels (1.5% reduction) but their use is associated with better long term glycemic control. The major adverse effect of sulfonylureas is hypoglycemia, with severe episodes accompanied by coma or seizures being infrequent and more common in elderly patients [6].

Glinides

Glinides such as repaglinide and nateglinide stimulate insulin secretion as sulphonylureas but they have more rapid onset of action and shorter duration of action than sulphonylureas. However, glinides bind to a different site within the sulfonylurea receptor and their use necessitates more frequent administration to overcome their short circulating half-life [4].

Thiazolidinediones (TZDs or Glitazones)

TZds such as pioglitazone and rosiglitazone act by increasing the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin. The effects of TZds on the glycemic control start to appear within 3 weeks of starting therapy with full effect appearing after 12 weeks [7]. Because TZds are mostly used as part of combination therapy, data on glycemic effects of monotherapy are limited, with HbA1c reductions reported to be in the range of 0.5% to 1.4%. The most common adverse effects associated with TZds include weight gain and fluid retention manifested as peripheral edema, although new or worsened heart failure may occur [4].

Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors such as acarbose decrease the rate of digestion of polysaccharides in the proximal small intestine, thus lower postprandial blood glucose levels without causing hypoglycemia. These agents are less effective in lowering blood glucose levels than metformin or sulfonylureas and reduce HbA1c by 0.5% to 0.8%. They are usually associated with increased gas production and other gastrointestinal disturbances because they increase delivery of incompletely digested carbohydrates to the colon. Their main uses include amelioration of postprandial hyperglycemia and prevention of the development of DM in high-risk patients with impaired glucose tolerance [8].

Insulin

Insulin is the most effective agent of all the antidiabetic medications in lowering glycemia, and will reduce the elevated HbA1c to, or close to, the therapeutic levels. In type 2 DM, it is usually used after failure of other medications to achieve a proper control of blood glucose levels. However, compared with insulin doses used in type 1 DM, relatively large doses (> 1 unit/kg) may be needed to overcome the insulin resistance that is seen in type 2 DM [2].

Recently introduced lines of therapy of type 2 DM

Dipeptidyl peptidase (DPP)-4 inhibitors

The incretins such as glucagon-like peptide 1 (GLP1) are mainly secreted by the intestinal L-cells, increase insulin secretion and inhibit glucagon production in response to nutritional stimuli. These effects are the basis for treatment with inhibitors of DPP4 in patients with type 2 DM [9]. Agents that inhibit DPP4 enzyme such as sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin can increase the active levels of incretins, thus improving the glycaemic control in type 2 DM. They are usually used as monotherapy in patients inadequately controlled by diet and exercise, and dual therapy in combination with metformin, TZDs and insulin. Generally, DPP4 inhibitors are well tolerated with a low risk of producing hypoglycemia, and maintain the patient's weight [10].

Sitagliptin was approved for treatment of type 2 DM in many countries and can be used alone or in combination with sulfonylurea, metformin or TZD. Monotherapy with sitagliptin was associated with significant reduction in HbA1c levels. In dual therapy studies, sitagliptin was as effective as glipizide in patients inadequately controlled with metformin. With sitagliptin, there was less hypoglycemia and less weight gain than with glipizide. Saxagliptin is approved as a drug for home treatment of type 2 DM or as a part of the combination therapy for patients not controlled with sulfonylureas, metformin or TZD [11]. Linagliptin is eliminated mainly through the enterohepatic system so it is not necessary to adjust the dose in patients with renal or hepatic impairment. Inducers of CYP3A4 or P-glycoprotein (e.g., rifampicin) may reduce the effectiveness of this agent [10].

DPP4 inhibitors are considered safe since both the risk of hypoglycemia and other adverse effects are rare. All of them are at increased risk of hypoglycemia when combined with sulfonylureas or insulin [12]. In comparative studies, there was no observed significant difference between them in the risk of hypoglycemia. Vildagliptin and alogliptin were reported to cause rare cases of hepatic dysfunction. At present, there is no sufficient data about whether DP4 inhibitors have the risk of causing acute pancreatitis. They should be discontinued in patients with persistent severe abdominal pain. Other reported side effects include headache, GIT disturbances, nasopharyngitis and upper respiratory tract infections [10].

Sodium glucose co-transporter-2 (SGLT2) inhibitors

SGLT2 inhibitors prevent renal reabsorption of glucose, increase its excretion and ameliorate hyperglycemia in patients with type 2 DM. The increase in glucose excretion and diuresis produced result in reduction of body weight and blood pressure. SGLT2 is located in the proximal renal tubules and is responsible for about 90% of glucose reabsorption [13]. SGLT2 inhibitors block the SGLT2 transporter in the proximal tubule, thus decrease glucose reabsorption and increase its excretion in urine. Because this process is independent of insulin action, there is low risk for hypoglycemia and no risk of fatigue or overstimulation of beta cells of the pancreas. Due to the nature of this mechanism of action, the efficiency SGLT2 inhibitors is lower in patients with renal dysfunction. The most representative members of this group include dapagliflozin, canagliflozin and empagliflozin [14].

Adverse effects of SGLT2 inhibitors include glucosuria which may increase the incidence of urogenital tract infections especially in women and uncircumcised men. Genital mycotic infections in women include vulvovaginal candidiasis, vulvitis, vulvovaginitis, and vulvovaginal mycotic infections. In male patients, balanitis and balanoposthitis might occur [15]. Other adverse effects of these agents include orthostatic hypotension and volume depletion due to excess diuresis. The risk of development of hypoglycemia with the use of SGLT2 inhibitors is minimal and occurs usually when combined with sulfonylureas or insulin [14].

Glucagon-like peptide-1 receptor agonist (RA-GLP1)

Human GLP1 is secreted in response to food intake and stimulates insulin release. Two incretins have been identified: GLP1, which is produced and released mainly by L-cells located in the intestine and gastric inhibitory peptide (GIP) which is secreted by enteroendocrine

K-cells in the proximal GIT. GLP1 treatment in type 2 DM patients increased insulin secretion and decreased secretion of glucagon, slowed gastric emptying, raised satiety and reduced food intake. GLP1 also may protect against myocardial ischemia as it promotes endothelium-independent artery relaxation protecting against endothelial dysfunction [16]. Also, it may improve renal functions by increasing diuresis and natriuresis. All of these actions may lower blood pressure and have positive effects on cardiovascular risk markers such as plasminogen activator inhibitor and brain natriuretic peptide. The use of GLP1 therapy is limited by its rapid breakdown by DPP4 enzyme [17].

Multiple RA-GLP1 had been developed with the beneficial effects of GLP1 with extended duration of action. RA-GLP1 agonists have proven efficacy for lowering HbA1c, fasting plasma glucose, body weight and systolic blood pressure, with a lower risk of hypoglycemia. They may be used in combination with metformin, sulfonylureas, TZD or insulin. RA-GLP1 are classified into short acting such as exenatide twice daily and lixisenatide or long-acting such as liraglutide, once-weekly formulation of exenatide LAR, albiglutide and dulaglutide [18].

Exenatide monotherapy lowered HbA1c by 0.7% - 0.9% and fasting plasma glucose by 17.5 - 18.7 mg/dL. The efficacy and safety of exenatide has been proven in several clinical studies. When compared exenatide with insulin glargine or biphasic insulin as part in patients with type 2 DM not controlled with oral agents, there were similar reductions in HbA1c in the exenatide and insulin groups suggesting non-inferiority of exenatide compared to insulin in relation to HbA1c reduction [19]. Exenatide showed weight loss and reduction in postprandial blood glucose levels compared with any insulin therapy, and lower rate of nocturnal hypoglycemia compared with insulin glargine. Administration of exenatide LAR had been proven to be more effective than highest dose of exenatide twice-daily, sitagliptin and pioglitazone, and insulin glargine in type 2 DM patients treated with oral hypoglycaemic drugs [20].

The major adverse effects of RA-GLP-1 are gastrointestinal disturbances including nausea, vomiting and diarrhea. All types of RA-GLP-1 should not be used in patients with history of pancreatitis and are not approved for use in type 1 DM. Exenatide and lixisenatide should not be utilized in patients with renal impairment and with severe gastrointestinal disturbances [21]. Liraglutide, albiglutide and dulaglutide should not be used in patients with personal or family history of medullary thyroid cancer. The risk of hypoglycemia is minimal, and may occur when RA-GLP-1 is combined with other drugs that cause hypoglycemia. Injection site reactions are more common with RAGLP-1 than with insulin [18].

Colesevelam

Colesevelam is a second-generation bile acid sequestrant that reduces LDL cholesterol in patients with hypercholesterolemia. It interferes with glucose absorption in the gastrointestinal tract. Colesevelam may be added to oral hypoglycaemic agents or insulin resulting in reduction of HbA1c levels of 0.5% in type 2 DM. Adverse effects associated with colesevelam therapy include nausea, vomiting, constipation and dyspepsia. Also, it may increase serum triglyceride concentrations by about 15-20%. It is not recommended to use colesevelam to treat type 2 DM patients due to the modest glucose-lowering effectiveness, the high financial cost and the limited clinical experience [22].

Bromocriptine

Bromocriptine is a dopamine agonist that has been used for the treatment of hyperprolactinemia and Parkinson's disease. Its mode of action in reducing blood glucose level is not yet completely understood. A quick release formulation of bromocriptine (Cycloset) was approved by the FDA for treatment of patients with type 2 DM. In short-term clinical trials in type 2 DM patients, bromocriptine when used as monotherapy or in combination with sulfonylureas was able to reduce HbA1c levels by 0.4% - 0.5% compared with the placebo. Nausea, vomiting and headache are frequently occuring adverse effects with bromocriptine therapy [23].

Pramlintide

Pramlintide is an amylin analogue that is administered by mealtime subcutaneous injection. It is only used in patients taking prandial insulin. Pramlintide replicates amylin actions and controls postprandial blood glucose levels without causing weight gain. Pramlintide

acts by slowing gastric emptying, promoting satiety and reducing the postprandial glucagons increase in patients with diabetes. These effects are glucose-dependent [24]. Pramlintide does not cause hypoglycemia in absence of other drugs that may cause hypoglycemia. The most frequent side effect of pramlintide is nausea which generally disappears by four weeks of therapy. Pramlintide should not be administered to patients with unawareness of severe hypoglycemia [25].

Future lines of therapy of type 2 DM

Unfortunately, all anti-diabetic agents have many adverse effects and are expensive. Therefore, searching for novel antidiabetic regimens with less adverse effects and less cost than the traditional agents is a major challenge for researchers [9].

Smart insulin patch

Smart insulin patch is a thin square covered with more than 100 tiny needles. The patch made of biocompatible materials that act faster and is easy to use [9]. The patch consists of small painless needles that are packed together with insulin and glucose-sensitive enzymes in microscopic storage units. The patch releases these enzymes when blood glucose level increases. It is suggested that this patch could have a long duration of action in diabetic patients that may confer better control of blood glucose level [26].

Polyphenols

Natural products containing high levels of polyphenol such as red grapes, apricots, coffee, eggplant, cocoa and green tea can regulate glucose metabolism through different pathways, such as restoring the integrity of beta cells of the pancreas, enhancing insulin releasing activity, and increasing glucose uptake by different body cells which can improve insulin resistance [27].

Dual-acting peptide

GLP1 and GIP are the two main incretin hormones that are released from the intestine in response to nutritional stimuli. Both hormones stimulate glucose-dependent insulin secretion. It was suggested that anti-obesity effect of GLP1 can be enhanced by co-administration with the incretin hormone GIP. In type 2 DM patients, there was a dose-dependent reduction of HbA1c, being -0.53% in patients treated with 4 mg of the dual agonist, and -1.11% in those treated with 30 mg, compared with placebo (-0.16%) [28]. The pharmacokinetics and pharmacodynamics results of coactivation of GLP1 and GIP receptors are considered as a promising novel strategy for treatment of obese type 2 DM patients, to prolong the activity of GLP1 and GIP dual agonists, and for the future development of a possible once-weekly GLP-1 and GIP dual agonists for treatment of type 2 DM [29].

Basal insulin analogues with glucagon-like peptide-1 mimetics

The combination of GLP1 mimetics with basal insulin analogues was reported to decrease the risk of hypoglycemia and weight gain induced for intensive insulin regimens in type 2 DM patients. Preliminary evidence suggests that the addition of basal insulin to a GLP1 mimetic with or without oral therapy, produce improvement in basal and postprandial blood glucose levels with less weight gain and reduced risk of hypoglycemia [30]. The fixed combination of insulin degludec and liraglutide (IDegLira) was proven to effectively lower HbA1c levels in patients with early or advanced cases of type 2 DM. LixiLan is a new once-daily single injection fixed-ratio combination of lixisenatide, and insulin glargine. Results from the Lixilan-L trial, showed that LixiLan demonstrated a statistically significant reduction in HbA1c levels compared with insulin glargine [31].

Oral RA-GLP1

Currently, RA-GLP1s are available only as injectables, either once daily or once weekly. Semaglutide is an oral long acting RA-GLP1 that is also developed as a once weekly injectable form. An oral semaglutide form leading to higher solubility and protection from enzymatic degradation is also being developed and is under investigations for efficacy in management of type 2 DM [32].

G protein-coupled receptor 119

G protein-coupled receptor 119 (GPR119) agonists is a G protein-coupled receptor that is expressed mainly in the pancreas and GIT. Activation of this type of receptors leads to reduction in food intake and body weight gain [28]. Moreover, GPR119 was shown to regulate incretin and insulin secretion. New agents acting on these receptors had been suggested as novel lines of treatment of obesity and diabetes. Co-administration of GPR119 agonists and DPP4 inhibitors may represent a novel therapeutic line for treatment of type 2 DM [33].

Oral insulin

Oral administration of insulin may have a more physiological action than parenteral insulin. Due to its first pass through the liver, it reduces glycogenolysis, hepatic glucose production and the risk of hypoglycemia, compared with parenteral insulin [34]. Currently, the data obtained from the human trials suggest that it could be a promising approach to the management of DM. Types of oral insulins in development include short-acting insulins as ORMD-0801 (Oramed) and Capsulin (Diabetology) in phase 2 studies, and the IN-105 (Biocon) in phase 3 studies and basal insulins, such as the OI287GT (NN1956) (NovoNordisk) [28].

Dual inhibition of SGLT1 and SGLT2

Sotagliflozin is a dual inhibitor of SGLT1 and SGLT2 with approximately 20-fold selectivity for SGLT2 over SGLT1. Recent studies showed that sotagliflozin increases urinary glucose excretion, delivery of glucose to the caecum, increases postprandial GLP1 and peptide YY release, with resultant reduction in postprandial blood glucose levels [35]. Sotagliflozin was evaluated in patients with type 2 DM not controlled with metformin. Sotagliflozin reduced fasting plasma glucose and HbA1c with a modest urinary glucose excretion, compared with selective SGLT2 inhibitors. Also, recent studies had suggested that combination of sotagliflozin with DPP4 inhibitors may represent a promising therapeutic modality for treatment of patients with type 2 DM with renal impairment [36].

Conclusion

While metformin is the mainstay of pharmacological therapy of type 2 DM, there is an increasing development of second and third-line oral and injectable drugs including sulfonylureas, meglitinides, insulin, TZD, alpha-glucosidase inhibitors, RA-GLP1 receptor agonists, DPP4 inhibitors and SGLT2 inhibitors. Also, insulin analogues that can better simulate endogenous insulin secretion and better regulate blood glucose levels had been used. The use of these agents should be individualized according to the degree of hyperglycemia, the presence of risk factors, patient preference and the possible adverse effects of the treatment. Although up till now there is no drug that can completely cure type 2 DM, novel agents with wide safety margin and acceptable efficacy that will improve the quality of life of patients with type 2 DM are developing.

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