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Pharmacological Management of Diabetes Mellitus

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Abstract: Diabetes is a chronic disease with no cure (except experimentally in type I diabetics), but it can be managed effectively. Conventional management of this disease includes lifestyle modifications such as losing weight, diet and exercise to long-term pharmacological use of oral hypoglycemics and/or insulin therapy. This review explores the use of oral hypoglycemic agents in management of diabetes mellitus.

Key words: Diabetes Mellitus, Oral Hypoglycemic Agents, Biguanides, Sulphonylureas, Meglitinides, A-Glucosidase Inhibitors, Thiazolidinediones, Insulin Therapy.

INTRODUCTION:

Diabetes mellitus is a chronic metabolic disorder in the metabolism of carbohydrates, proteins and lipids. It is often accompanied after a period of time by specific microvascular, macrovascular and neuropathic complications [1]. All these emanate from insufficient secretion of insulin by the pancreas or improper utilization of insulin by target cells [2].

The goal for diabetes management is to avoid or minimize chronic diabetic complications, as well as to avoid acute problems of hyperglycemia or hypoglycemia, blindness, heart disease and limb amputation. Full-blown diabetes mellitus type II can be evaded in those with only mildly impaired glucose tolerance [3].

Patients with type I diabetes mellitus require direct injection of insulin as their bodies cannot produce enough (or even any) insulin. For type II diabetics, diabetic management consists of a combination of diet, exercise, and weight loss, in any achievable combination depending on the patient. Patients who have poor diabetic control after lifestyle modifications are typically placed on oral hypoglycemics. Some type II diabetics fail to respond to these and must proceed to insulin therapy [3,4].

The Role of Glucose-lowering Agents in Management of Diabetes Mellitus:

1. **Oral Hypoglycemic Drugs:** Pharmacological treatment of diabetes mellitus is indicated when fasting glucose level exceeds 1600mg/L. The oral glucose-lowering drugs are used for management of type II diabetes mellitus. Conventionally, oral therapy is indicated in any type II diabetic in whom diet and exercise fail to achieve acceptable glycaemic control. However, although initial responses may be good, oral hypoglycaemic agents lose their effectiveness in a good number of diabetics [5]. These oral hypoglycaemic agents are discussed here below:

i. **Sulphonylureas:** These agents reduce blood glucose by increasing insulin secretion from pancreatic β-cells in patients with residual β-cell function. All are well absorbed and their half-life and duration of action vary by agent. They include the first generation agents like chlorpropamide (Diabinese), tolbutamide (Orinase), tolazamide (Tolinase), and acetohexamide (Dymelor), the second-generation agents like glyburide (DiaBeta, Micronase, PresTab, or Glynase) and glipizide (Glucotrol or Glucotrol XL), and the third generation agents like glimepiride (Amaryl). They all cause mild hypoglycaemia but severe hypoglycaemia is less common [6].

Acutely, sulphonylureas stimulate insulin secretion by the pancreatic β-cell. Chronically, they increase the sensitivity of β-cell, tissue glucose uptake, and decrease gluconeogenesis [7]. Patients who respond best to treatment with sulphonylureas include those with a diagnosis of type II diabetes before 40 years of age, duration of disease less than five years before initiation of drug therapy and a fasting blood glucose level of less than 3000mg/L [8].

Approximately two thirds of patients who begin therapy with a sulphonylurea respond favourably. However, up to 20% of them require additional medication. Few patients with uncontrolled diabetes receive clinical benefit when switched from one sulfonylurea agent to another [8]. The use of agents with a longer half-life such as chlorpropamide in the elderly and in patients with renal impairment is discouraged because the risk of hypoglycaemia is increased [9].

In addition, the side effects of sulphonylureas include hypothyroidism and thyromegaly (through inhibition of organic iodine binding), cardiovascular disorders, skin infections, hematological disorders, cholestatic jaundice, hyponatremia, and water retention. Besides, sulfonylurea therapy is associated with weight gain due to hyperinsulinemia [10], which has been implicated as a cause of secondary drug failure [5,8,10].

ii. **Biguanides:** These agents increase the sensitivity of insulin by decreasing hepatic gluconeogenesis (primary effect), increasing skeletal muscle glucose uptake, reducing plasma triglycerides and LDL-Cholesterol levels and increasing peripheral insulin sensitivity (secondary effect). They do not increase insulin levels or cause weight gain. Taken alone, they do not cause hypoglycemia [6,11].

An example of biguanides is metformin (phenformin), originally derived from a medicinal plant *Galega officinalis*. It is used as monotherapy or in combination with sulfonylureas for management of type II diabetes mellitus. When used as monotherapy, metformin does not cause

hypoglycemia and is thus termed an antihyperglycemic. The use of metformin is contraindicated in patients with renal insufficiency (i.e., a serum creatinine level of 15mg/L in men and 14mg/L in women, or abnormal creatinine clearance) or acute or chronic metabolic acidosis [12].

Cimetidine (Tagamet) decreases the renal clearance of metformin and potentiates its effects. Patients receiving oral anticoagulant therapy and metformin require a higher dosage of warfarin (Coumadin) to achieve a therapeutic antithrombotic effect [13]. However, side effects of metformin are weakness, fatigue, shortness of breath, nausea, dizziness, lactic acidosis, and kidney toxicity [11].

iii. **α-Glucosidase Inhibitors (α-Gis):** α-glucosidase inhibitors, such as Acarbose (Precose) and Miglitol (Glyset), are indicated as monotherapy or in combination with sulfonylureas for management of type II diabetes. These agents decrease post-prandial glucose levels by inhibiting the breakdown of complex carbohydrates and delay the absorption of monosaccharides from the gastrointestinal tract [14]. They inhibit the action of α-glucosidase, the enzyme responsible for digesting carbohydrates, in the intestine, thus delaying and attenuating postprandial blood glucose peaks. Undigested sugar is delivered to the colon, where it is converted into short-chain fatty acids, methane, carbon dioxide, and hydrogen [6].

α-GIs do not increase insulin levels or inhibit lactase (lesser effect on fasting levels). They do not cause weight gain and restore ovulation in women with an ovulation due to insulin resistance. Used alone, α-GIs do not cause hypoglycemia. Less than 2% is absorbed as active drug. They can be used as monotherapy or combined with a sulfonylurea agent, a thiazolidinedione, metformin, or insulin. They are taken with food to minimize adverse effects [15].

Acarbose and miglitol are titrated over two to three weeks to minimize flatulence and other gastrointestinal side effects that lead to discontinuation of these agents. α-glucosidase inhibitors are contraindicated in patients with inflammatory bowel disease, partial intestinal obstruction, a predisposition to intestinal obstruction, colonic ulceration and other gastrointestinal disorders [14].
Dose-dependent hepatotoxicity is associated with this drug class; so liver function tests are carefully monitored in patients receiving higher dosages of these medications (for example, more than 50 mg three times daily). Transaminase elevations are reversible with discontinuation of the drug and are often asymptomatic. Serum transaminase levels are checked every three months for the first year patients take the medication and periodically thereafter. Drugs that are susceptible to binding with other agents (for instance, cholestyramine [Questran]) are taken two to four hours apart from α-glucosidase inhibitors to avoid drug interactions. Intestinal absorbents and digestive enzyme preparations are not administered with acarbose [9]. However,their major side effects are gas, bloating and diarrhoea [11].

iv. **Thiazolidinediones:** Thiazolidinediones are a unique drug class of "insulin sensitizers" that promote skeletal muscle glucose uptake [16]. They improve insulin sensitivity in muscles and in the liver, decreasing plasma triglyceride levels, but such decreases are associated with weight gain and an increase in LDL-cholesterol levels. They are very expensive agents [5]. These drugs work by binding to peroxisome proliferator-activator receptor-γ (PPAR-γ), which is primarily located on adipocytes [17]. In type II diabetic patients, thiazolidinedione therapy is associated with a reduction in circulating

plasma free fatty acid (FFA) levels and FFA turnover [18], a shift in fat distribution from visceral to subcutaneous fat storage depots [18,19,20], a decrease in hepatic fat content, and an improvement in peripheral insulin sensitivity [21].

However, no previous study has examined whether the decrease in hepatic fat content and/or plasma FFA concentration is related to improved splanchnic glucose uptake (SGU) following thiazolidinedione treatment in patients with type II diabetes mellitus [22]. They include such drugs as troglitazone, rosiglitazone and pioglitazone. Troglitazone (Rezulin) is the first agent of this drug class to be introduced in the market and it reduces insulin resistance [4].

Troglitazone is beneficial in patients requiring large daily amounts of insulin (more than 30 units per day) whose diabetes is still uncontrolled. A reduction of up to 50% in total daily insulin dosage is possible with drug titration. Troglitazone is also effective when used in combination with other oral agents, thereby potentially delaying the need to start insulin therapy [23].

The US Food and Drug Administration recently ruled in March 2000, that troglitazone should only be used in combination with other diabetic therapies. The effectiveness of oral contraceptives is decreased with troglitazone administration. Over 150 case reports of hepatotoxicity have been reported with troglitazone, so liver function is monitored every month for the first eight months of treatment and every other month for four months thereafter [16].

Rosiglitazone (Avandia) is an insulin sensitizer with major effect in stimulation of glucose uptake in skeletal muscle and adipose tissue. It lowers plasma insulin levels. It is used for treatment of type II diabetes associated with insulin resistance [24].

Pioglitazone (Actos) improves target cell response to insulin without increasing insulin secretion from pancreas and it decreases hepatic glucose output and increases insulin-dependent glucose use in skeletal muscle and liver [6].

v. **Meglitinides:** These agents are short-acting insulin secretagogues. They act on the ATP-dependent potassium channels in pancreatic β-cells, allowing opening of calcium channels and increased insulin release [6].

They include the drug repaglinide (Prandin), which is a benzoic acid derivative and the first of the non-sulfonylurea meglitinide introduced in early 1998. The mechanism of action and side effect profile of repaglinide are similar to those of the sulfonylureas. This agent has a rapid onset of action and is taken with meals two to four times daily. Repaglinide is a suitable option for patients with severe sulfa allergy who are not candidates for sulphonylurea therapy. The drug is used as monotherapy or in combination with metformin. It is titrated cautiously in elderly patients and in those with renal or hepatic dysfunction [16]. The side effects of repaglinide include weight gain, gastrointestinal disturbances, and hypoglycaemia [10].

2. **Insulin therapy:** Insulin is added to an oral agent when glycemic control is suboptimal at maximal doses of oral medications. Some diabetologists prefer to initiate insulin therapy in patients

with newly diagnosed type II diabetes [5]. Weight gain and hypoglycemia are common side effects of insulin therapy [11,25]. Vigorous insulin treatment also carries an increased risk of atherogenesis [24].

Patients with type I diabetes require lifelong treatment with insulin to promote glucose utilization. Short-, intermediate-, and long-acting insulin preparations are used. Pork, beef, and beef-pork insulins were used previously, but at present, recombinant human insulin is used. Commercially prepared mixtures of 70/30 and 50/50 insulin (70% NPH + 30% regular and 50% NPH + 50% regular insulin, respectively) are also used. Optimal diabetic control requires frequent self-monitoring of blood glucose. Frequent monitoring allows for rational adjustments in insulin doses. Most patients with type I diabetes require at least a split/mixed insulin regimen (for example, NPH/regular combination before breakfast and supper) [6].

Increasingly, a multiple injection regimen, in which regular or lispro insulin is adjusted before each meal and intermediate-acting insulin given at bedtime, is used to provide more flexibility and achieve better glycemic control. With a multiple injection regimen, patients add or subtract regular or lispro insulin (called compensatory doses) from their basic insulin dose in response to the immediate blood glucose level before the meal [6].

All the insulins are contraindicated in hypoglycaemia and hypersensitivity but they are safe in pregnancy. Dose adjustment is necessary in patients with renal or hepatic dysfunction. Medications that decrease hypoglycaemic effects of insulin include acetazolamide, AIDS antivirals, asparaginase, phenytoin, nicotine, isoniazid, diltiazem, diuretics, corticosteroids, thiazide diuretics, thyroid replacement, estrogens, ethacrynic acid, calcitonin, oral contraceptives, diazoxide, dobutamine, phenothiazines, cyclophosphamide, dextrothyroxine, lithium carbonate, epinephrine, morphine sulfate, and niacin [26].

Medications that increase hypoglycaemic effects of insulin include calcium, ACE inhibitors, alcohol, tetracyclines, β-blockers, lithium carbonate, anabolic steroids, pyridoxine, alicylates, monoamine oxidase inhibitors (MAOIs), mebendazole, sulfonamides, phenylbutazone, chloroquine, clofibrate, fenfluramine, guanethidine, octreotide, pentamidine, and sulfinpyrazone [26].

CONCLUSION:

Oral hypoglycemic agents and insulin therapy have remarkable significance in management of diabetes mellitus. Sadly, it is document in literature that all these agents are bedeviled by adverse effects arising from their usage. This should invoke the interest of scientists particularly in diabetology and pharmacology to engage in efforts aimed at developing safer but equally effects agents. Biotechnology and genetic engineering can also aid in these efforts. Literature is also rich with information that some medicinal plants have been found to be hypoglycemic. Indeed, as seen in this review, some of the conventionally used antidiabetic agents are plant-derived. Perhaps, pharmacognosy may also be of help in this regard.

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