Chapter 6

Pharmacological Treatments for Type 2 Diabetes

Roberto Pontarolo, Andréia Cristina Conegero Sanches, Astrid Wiens, Cássio Marques Perlin, Fernanda Stumpf Tonin, Helena Hiemisch Lobo Borba, Luana Lenzi and Suelem Tavares da Silva Penteado

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1. Introduction

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, which is defined as a chronic metabolic disorder characterized by hyperglycemia. In this disease, the body is able to produce insulin; however, its secretion is irregular and/or the body's cells fail to use and respond appropriately to this hormone (insulin resistance), leading to an accumulation of blood glucose [1, 2].

Although the reasons for the development of T2DM are still unknown, it is a multifactorial disease that involves a genetic predisposition as well as other factors, including a poor diet, sedentary lifestyle, age (45 or older), previous gestational diabetes, and overweight or obese physical conditions, which represent the most common risk factors for the development of insulin resistance [3, 4].

Epidemiologically, the number of individuals with T2DM (representing 85-95% of all cases of diabetes mellitus) in recent decades has increased rapidly worldwide. This disease usually affects adults, especially males, but an increase in the number of cases in children and adolescents has also been observed [5, 6]

The high incidence of T2DM is associated with economic development, aging populations, increasing urbanization, dietary changes, reduced physical activity and changes in lifestyle and other cultural patterns. It is estimated that more than 382 million people suffer from this disease worldwide (8.3% prevalence). In 2013, 5.1 million deaths were reportedly caused by diabetes. If these trends continue, it is estimated that by the year 2035, approximately 592 million people (1 in 10 adults) will be carriers of the disease [7-9].

Therefore, the increasing number of new cases of diabetes per year combined with high prevalence and mortality rates impose high costs socially and economically to the populations of all countries. In 2013, approximately 548 billion dollars were spent worldwide on diabetic patients. Thus, understanding this disease and all the variables involved, including prevention, diagnosis and treatment must be a priority [8].

The diagnosis of T2DM is based on summarized plasma glucose quantification criteria (either fasting or after a glucose tolerance test). Furthermore, the assessment of the amount of glycated hemoglobin (Hb_{A1c}) is included as a diagnostic option for diabetes. However, many individuals with T2DM are asymptomatic in the early stages of this disorder and only discover the disease after the onset of more severe symptoms and other complications. The first symptoms of T2DM may include polyuria, polydipsia, constant hunger, appearance of wounds with delayed healing, visual changes and frequent infections [10, 11].

When undiagnosed or poorly controlled, this disease is a risk factor for the onset of various complications at both the microvascular (nephropathy, retinopathy and neuropathy) and macrovascular (cardiovascular disease) level. Diabetes is one of the major factors that leads to blindness, kidney failure, lower limb amputation and development of cardiovascular disease, the latter being the primary cause of death worldwide [3, 11].

Therefore, simple lifestyle changes, including increased physical activity, diet modification and weight loss are recommended for the management of pre-diabetes and early diabetes. These changes have been shown to be effective in preventing or delaying the progression of T2DM or damage to target organs [4, 12].

The treatment of diabetes mainly targets glycemic control, thus aiming to relieve symptoms, improve the quality of life of patients, prevent further complications and reduce mortality. However, the use of other therapeutic treatments is needed as a strategy for reducing multifactorial risks [3, 13].

The basic strategies for the treatment and control of diabetes mostly consist of a specific balanced diet, physical activity and proper use of medications (oral and/or insulin agents). Patient education coupled with self-care and support from family and physicians are essential procedures for the prevention of acute complications and reduction of long-term complications. Additionally, frequent tests (including blood pressure measurement and lipid profile), foot care (avoiding the appearance of lesions), stress control and reduction in the consumption of alcoholic beverages and tobacco are important actions related to disease control [1, 14, 15].

Compared with type 1 diabetes mellitus patients, the majority of type 2 patients typically do not require daily insulin doses. The disease can be treated with oral medications and changes in lifestyle until resistance becomes difficult to control, after which an insulin regimen is usually required [8].

Thus, drug treatment of T2DM is based on the knowledge of patient characteristics together with the severity of the hyperglycemia and availability of therapeutic options. Many oral drugs are used to control diabetes, such as metformin (biguanide), sulfonylureas and thiazolidinediones, which have been used for decades with satisfactory results. These antidiabetic drugs

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compose the most studied cast of oral pharmacologicals worldwide and play an important role in glycemic control; in addition, they are often recommended as the first option for the treatment of the disease by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) [10, 15, 16]. Technological advances and new avenues of drug research have enabled the development of new drug therapies for the treatment of T2DM, and approximately 180 new drugs are currently under study [17, 18].

Typically, various drug classes can be used to control type 2 diabetes, including human insulin analogs, drugs that reduce insulin resistance (biguanides and thiazolidinediones or glitazones), secretagogues and their analogues (sulfonylureas, meglitinides, inhibitors of dipeptidyl peptidase IV (DPP-4) or agonists and analogues of glucagon-like peptide-1 (GLP-1)), and drugs that reduce the rate of carbohydrate degradation (alpha-glucosidase inhibitors). Dapagliflozin is one of the newer medications for glycemic control and was recently approved by the FDA (January 2014). Its mechanism of action inhibits the sodium-glucose cotransporter 2 (SGLT2), a protein responsible for glucose reabsorption in the kidney, which leads to the elimination of excess glucose in the urine [17, 18].

Multiple therapies, or a combination of oral hypoglycemic drugs and/or other drugs, are also an option for the control of diabetes mellitus [11, 19]. However, the therapeutic use of drugs is limited by factors such as their efficacy, adverse events, costs, side-effects, dose management problems, inflexible dosages, weight gain, etc.; therefore, such effects should be critically evaluated for each patient [19].

For example, weight loss is a priority in obese diabetics. If glycemic control is not achieved after 4-6 weeks of treatment with drugs that increase sensitivity to insulin action (such as biguanides and thiazolidinediones) medications may be given to control obesity, which include drugs that affect the appetite and induce satiety, such as orlistat. If necessary, drugs may also be used that retard the degradation of sugars in the diet (such as acarbose or miglitol) or drugs such as sulfonylureas or meglitinides that increase insulin secretion in the pancreas [20-23].

In terms of therapeutic classes, the action of biguanides, whose main representative is metformin, is related to decreased peripheral insulin sensitivity, reduced hepatic glucose output, and modified lipid metabolism. All of these effects contribute to the control of T2DM. The advantages of these drugs include the absence of hypoglycemia and its anorectic effect, which also aids in patient weight loss. The adverse effects of this class are few but include diarrhea, nausea, metallic taste and intestinal colic, which gradually decreases with continued use [16, 19, 23].

The class of sulfonylureas that act by directly stimulating insulin secretion (secretagogues) includes chlorpropamide, glibenclamide, gliclazide and glimepiride. These drugs have several adverse effects, including nausea and vomiting (gastrointestinal), hypoglycemia (glucose), leukopenia, agranulocytosis, thrombocytopenia and hemolytic anemia (hematological) and weight gain. Accordingly, the use of newer insulin secretagogues (glinides class, including mitiglinide, repaglinide and nateglinide) is suggested as an alternative for patients treated with sulfonylureas who have irregular meal times or late postprandial

hypoglycemia. Because of their rapid absorption, the action of these drugs is initiated 30 minutes after administration [16, 22].

The thiazolidinedione drugs (pioglitazone and rosiglitazone) are oral hypoglycemic agents capable of increasing the sensitivity of liver, muscle and fat cells to insulin, which results in reduced peripheral resistance. This class is contraindicated in patients with hepatic dysfunction and heart conditions and adverse effects include upper respiratory tract infections, headaches, weight gain, anemia and edema [12, 16, 23].

With respect to alpha-glucosidase, competitive inhibitors such as acarbose, miglitol and voglibose act as antagonists of amylase and sucrose, thereby decreasing the intestinal absorption of glucose. These drugs are contraindicated in pregnant or lactating patients and in diabetic patients with renal or hepatic dysfunction [6, 18].

Another recent class of oral hypoglycemic drug is the DPP-4 inhibitors (sitagliptin, vildagliptin and saxagliptin), which act by increasing the levels of hormones that help to control glucose concentrations. These drugs have few adverse events, and incidences of hypoglycemia and weight gain are low [16, 23].

In addition to these oral medications, subcutaneous administration of exenatide (GLP-1 agonist) can stimulate insulin secretion (secretagogue). In addition to facilitating glycemic control, this medicine also helps in patient weight loss. Possible adverse events include nausea, vomiting and diarrhea [16, 23, 24]

For injectable drugs, the application of human insulin analogs (lispro, aspart and glargine) for the treatment of T2DM may be indicated for patients who no longer respond to diet combined with exercise and oral hypoglycemic agents or in more severe hyperglycemia cases. In addition to the different types of administration (including the innovation of inhalable insulin), this hormone may be used in combination with oral hypoglycemics [12, 25].

In short, with the emergence of new treatments for diabetes, various individualized treatment options are possible that consider ease of access, cost, mode of administration and patient characteristics.

Thus, the aim of this chapter is to evaluate the available treatments for T2DM as well as their mechanisms of action and adverse effects and describe the new drugs and therapeutic trends that are available. Such diabetes treatment updates for healthcare professionals and caregivers is essential for proper disease management and health promotion.

2. Biguanides

Metformin and phenformin are oral antidiabetic drugs of the biguanide class. Metformin is the drug of choice for the treatment of adults with type 2 diabetes because of its lower frequency of side effects. This drug is currently used by nearly one-third of the diabetic patients in Italy and is the most prescribed in the U.S. (> 40 million prescriptions in 2008). Phenformin is no longer marketed in many countries, although it is still available in Italy [26-28].

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Both metformin and phenformin increase weight loss in obese non-diabetic patients without substantially reducing blood glucose levels. This weight loss is attributed to the drugs' anorectic effect and a slight reduction in the gastrointestinal absorption of carbohydrates [29]. Phenformin was withdrawn from clinical practice in the 1970s because of a greater tendency to develop severe and fatal adverse events, such as lactic acidosis.

2.1. Metformin

Metformin is sold in 500 and 850 mg tablets, and the maximum dosage is 2.5 g/day, although there are reports in the literature of dosages up to 3 g, which are always administered after meals to minimize gastrointestinal side effects [30]. It has been reported that this drug increases the number and improves the affinity of insulin receptors both in adipocytes and muscle. In muscle, glucose uptake increases from 15 to 40% and gluconeogenesis is stimulated. In adipocytes, metformin inhibits lipolysis and the availability of free fatty acids (FFA). Furthermore, metformin improves insulin action in the liver by reducing hepatic glucose production from 10 to 30%, and at the cellular level, it increases the tyrosine kinase activity of the insulin receptor in the muscles, which stimulates GLUT4 translocation and the activity of glycogen synthetase [31].

The use of metformin also improves the lipid profile by decreasing triglyceride levels by 20-25%, LDL-cholesterol by up to 10% and plasminogen activation inhibitor (PAI-1) by 20-30% and increasing HDL-cholesterol by 17%. Insulin secretion to stimuli may remain unchanged or decrease, and its anorectic effect helps in weight loss. In addition to being associated with weight reduction, its effectiveness in glycemic control is similar to that of sulfonylurea [32]. Another advantage is the absence of hypoglycemia because insulin secretion is not stimulated [33].

The isolated use of metformin in type 2 diabetes lowers blood glucose levels by approximately 25%, or 60 to 70 mg/dl, and glycosylated hemoglobin by 1.5 to 2% [31]. Intensive glucose control using metformin significantly decreases the risk of cardiovascular disease and diabetes mellitus-related mortality and is associated with less weight gain and a lack of treatment-induced hypoglycemia associated with insulin or sulfonylureas [34].

Metformin is absorbed in the intestine, excreted by the kidneys and minimally metabolized by the liver. Metformin has a low affinity for mitochondrial membranes and does not interfere with oxidative phosphorylation, and it is indicated as a monotherapy in obese or even glucose intolerant diabetics. Approximately 5 to 10% of patients each year fail to have an appropriate response to this drug. In these cases, metformin can be used in combination with sulfonylurea, acarbose, thiazolidinediones, repaglinide and/or insulin to achieve satisfactory control [35-40].

The most common side effects of metformin are diarrhea (15%), metallic taste and nausea, which often decrease with continued use of the medication. The occurrence of lactic acidosis is rare (0.03 to 0.4/1000/year) and occurs most often in people who have a contraindication to metformin, such as chronic liver disease (elevated transaminases 2-3 times the normal values) and heart, respiratory, or renal conditions (clearance < 70 ml/min or serum creatinine ≥ 1.5 mg/dL). The use of metformin is not advisable in people over 80, pregnant women, infants or

alcoholics. In patients with proteinuria who are subjected to radiological examination containing iodine, it is prudent to provide adequate hydration and discontinue the medication a few days prior to such examinations [33]. This drug shows a synergistic effect with cimetidine and may decrease the absorption of vitamin B12 [30].

3. Thiazolidinediones

The thiazolidinediones (TZDs) are popularly known as glitazones, and representatives include the drug troglitazone (withdrawn from the market because of liver toxicity), rosiglitazone and pioglitazone (second generation TZDs).

TZDs are widely used in the treatment of type 2 diabetes and increase and sensitize insulin action in the liver, muscles and adipocytes, thereby decreasing peripheral resistance. They activate intracellular nuclear receptors (PPAR-gamma-peroxisome proliferator-activated receptor) that regulate the expression of genes encoding glucose and lipid metabolism and are responsible for glucose uptake mediated by insulin in the peripheral tissues and differentiation of preadipocytes into adipocytes. Additionally, these drugs inhibit peripheral lipolysis in adipocytes and assist in reducing the levels of free fatty acids and visceral adipose tissue, resulting in improved glycemic and metabolic parameters. These drugs show good results in terms of long-term glycemic control compared with other consecrated therapeutic options, such as sulfonylureas and metformin [41-43].

TZDs decrease glucose levels by approximately 20% but do not increase insulin secretion. They inhibit the oxidation of long-chain fatty acids in the liver, decreasing gluconeogenesis and the availability of free fatty acids. Although these drugs reduce triglycerides by 15 to 20% and increase HDL-cholesterol by 5 to 10%, the total cholesterol and LDL-cholesterol levels may not change or may increase from 10 to 15% [33]. When compared to metformin, troglitazone has a greater potentiating effect of peripheral insulin action and little effect on the reduction of hepatic glucose production. The association of thiazolidinedione with metformin is interesting because it produces additive effects [39].

TZDs also increase the expression of glucose transporters (GLUT4) and lipoprotein lipase and reduce the expression of leptin and tumor necrosis factor (TNF-alpha). These results make it one of the most widely prescribed classes for the treatment of T2DM [33, 44].

Side effects occur in less than 5% of patients, and they consist of upper respiratory tract infections, headaches, elevated transaminase levels, edema, weight gain and anemia. Hypoglycemia can occur when its use is concomitant with secretagogues or insulin. The drugs are contraindicated for use in children and pregnant women and in individuals with liver disease and elevated transaminase levels (2-3 times the reference values) [33].

3.1. Troglitazone

In mice subjected to arterial injury, troglitazone inhibited the growth of vascular smooth muscle cells and intimal hyperplasia, suggesting that TZDs decrease the progression of

atherosclerosis. Diabetic patients treated with troglitazone show decreases in platelet adhesion, activation of plasminogen activator inhibitor (PAI-1) and blood pressure levels. These multiple effects strengthen its indication for the treatment of the metabolic syndrome. However, caution is advised with troglitazone treatment because of possible liver complications, including fatal cases. In addition, caution is required when troglitazone is used with cardiac patients because of the possibility of edema [33, 45, 46].

3.2. Pioglitazone

Pioglitazone may be used as a monotherapy or in combination with metformin (increasing the anti-hyperglycemic effect), sulfonylurea, meglitinide, or even insulin, especially in diabetic patients with metabolic syndrome. The dose varies from 15 to 45 mg, which can be administered once a day. Pioglitazone displays a similar mechanism of action and side effects as rosiglitazone and less liver toxicity than troglitazone. However, it can interact with other drugs that are metabolized by P_{45} enzymes and alter their serum levels. An example is a decrease of approximately 30% of the contraceptive effect of ethinyl estradiol and norethindrone. Therefore, the contraceptive dose should be increased in diabetic women who do not wish to become pregnant. Its pharmacokinetics are not altered by mild to moderate renal impairment, so dose modification is required [47].

3.3. Rosiglitazone

Rosiglitazone is more powerful and has less liver toxicity than troglitazone. Additionally, it does not induce metabolism by cytochrome P_{450} (CYP) 3A4; thus, there is no interaction with oral contraceptives such as digoxin, ranitidine, nifedipine, etc. The rosiglitazone dose varies from 4 to 8 mg, which can be administered once a day. Similar to pioglitazone, rosiglitazone's pharmacokinetics are not altered by mild to moderate renal impairment, so dose modification is required [48].

Recently published safety data have raised concerns related to a possible association between the chronic use of rosiglitazone and increased risk of cardiovascular events, which is consistent with the use of TZDs in clinical practice. In addition, recently published studies have indicated that there is a loss of bone mass and increased possibility of fracture in patients using these medications [42, 44, 49].

4. Meglitinides

Insulin secretagogue agents act by stimulating endogenous insulin secretion via pancreatic β cells, and they include classes of sulfonylureas and meglitinides used in the treatment of T2DM. Meglitinide analogues consist of a relatively new class of oral hypoglycemic, and their clinical use in adult patients with T2DM was approved in 2000. These drugs were developed to promote the rapid increase in insulin secretion from β cells and therefore affect postprandial glucose levels. The mechanism of action of meglitinides is quite similar to that of sulfonylureas; however, meglitinide analogues have the advantage of a reduced risk of hypoglycemia because

of their shorter half-life. Meglitinides are secretagogues of short-acting insulin, and they act primarily on postprandial hyperglycemia. Because of their characteristics, the meglitinides are preferable to insulin secretagogues such as sulfonylureas, especially in elderly patients [50-53]. Representatives of the meglitinide class include repaglinide, nateglinide and mitiglinide derived from benzoic acid and the amino acid D-phenylalanine, whose action is initiated approximately 30 minutes after administration because of rapid absorption. The advantages of these drugs are that they have no interactions with other drugs and are not contraindicated in pregnancy, during lactation or in the presence of other pathologies [52, 54].

4.1. Repaglinide

Repaglinide was the first meglitinide analogue approved for use in adults with T2DM; it is the S(+) enantiomer of 2-ethoxy-4-(2-((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid and has a molecular weight of 452.6 Da [50]. Repaglinide stimulates insulin release in a rapid action style, thereby promoting a decrease in blood glucose levels. Because of the rapid action, repaglinide is one of the most commonly used antidiabetic drugs in patients who have high postprandial glycemia [55-57].

The mechanism of action by which the meglitinide analogue stimulates insulin secretion comes from blocking the ATP-dependent potassium channels (KATP) of pancreatic β-cells, which results in membrane depolarization and calcium influx through voltage-dependent calcium channels. This mechanism culminates in an increased influx of calcium into the β cells, which stimulates exocytosis of insulin-containing granules [50, 58].

With regard to pharmacokinetics, repaglinide, whose absorption is independent of concurrent food intake, is rapidly absorbed following oral administration with 63% bioavailability. The maximum concentration is reached approximately 45 minutes after administration (Tmax ~ 45 min), and the half-life of plasma elimination is relatively short (approximately 1 hour); therefore, the drug is eliminated from the body within 6 hours. The drug is metabolized in the liver via cytochrome P_{450} (CYP3A4), with approximately 90% of the metabolites excreted in the bile and only 8% secreted in the urine. Altogether, 2% of the drug is eliminated in an unchanged form, and because the metabolites are not biologically active, there is no effect on the blood glucose. There is a rapid elimination of repaglinide through the biliary tract and no apparent accumulation in the plasma after multiple doses [50, 59-61].

Hepatic metabolism via cytochrome P_{450} means that concentrations of repaglinide may be increased by concomitant use of substances that inhibit the CYP3A4 enzyme, such as certain antibiotics and steroids; however, the concomitant intake of CYP3A4-inducing agents, such as barbiturates and carbamazepine, can lead to an increased metabolism of the meglitinide analogue, thus reducing its concentrations [50, 59-61].

4.2. Nateglinide

Another insulin secretagogue agent that also belongs to the class of meglitinides corresponds to nateglinide. Similar to repaglinide, nateglinide ((N-[(trans-4-isopropylcyclohexyl)-carbonyl]-D-phenylalanine A-4166) phenylalanine derivative) acts through the inhibition of KATP

and causes the depolarization of the plasma membrane of β cells. This culminates in the influx of calcium ions into the cell and subsequent secretion of insulin [50, 62].

Despite the similar mechanism of action of these two meglitinide analogues, in vitro studies have demonstrated that nateglinide inhibits KATP channels faster and with a shorter duration of action than repaglinide. In addition, the half-life of repaglinide at the receptor of action is approximately 3 minutes, whereas the half-life of nateglinide is 2 seconds. Therefore, the time required for nateglinide to dissociate from the receptor is 90 times faster than that of repaglinide, so nateglinide has a very fast and ephemeral effect on insulin release. In vitro experiments have demonstrated that the action of nateglinide is enhanced in the presence of glucose compared to that glyburide and repaglinide, so that the response of the KATP channel with nateglinide is significantly less in periods of euglycemia than in periods of hyperglycemia. Thus, the minimum total insulin exposure generated by this meglitinide analogue protects the body against hypoglycemic attacks and allows the patient greater flexibility in relation to the intervals between meals. Pharmacodynamic studies have demonstrated that when nateglinide is administered before meals in type 2 diabetic patients, a secretion of early stage insulin occurs that causes a significant dose-dependent reduction in postprandial hyperglycemia [50, 59, 63].

Regarding its pharmacokinetic properties, nateglinide is absorbed rapidly, with peak plasma concentrations reached within 1 hour. This drug is rapidly eliminated from the plasma, with a half-life of 1.8 hour. Because of the short half-life, nateglinide is not accumulated at any administration dose. The drug is metabolized mainly via the cytochrome P_{450} (CYP2C9 and CYP3A4) and is eliminated via the kidneys, with 10% eliminated unchanged in the urine and 20% eliminated unchanged in the bile [50, 59, 64].

Both repaglinide and nateglinide may be used as a monotherapy or in combination with other agents, such as metformin and glitazones. The meglitinides have similar abilities in reducing fasting blood glucose, postprandial levels of plasma glucose and early insulin secretion, and they improve the insulin sensitivity and function of pancreatic β cells. However, repaglinide was more effective in reducing the glycosylated hemoglobin Hb_{A1c} and is also preferred to nateglinide in patients with chronic renal disease because nateglinide has active metabolites that are eliminated by the kidneys [52, 63].

4.3. Mitiglinide

Mitiglinide ((-)-2(S)-benzyl-4-(cis-perhydroisoindol-2-yl) butyric acid) is the third meglitinide analogue and corresponds to a benzylsuccinic acid derivative. It presents a similar mechanism of action to the other two meglitinide analogs, and its selective action on KATP channels of pancreatic β cells promotes insulin secretion with few adverse effects on the cardiovascular system [58, 59, 65]. Similar to nateglinide, mitiglinide is often used in early stage diabetes mellitus because it induces a rapid and short duration of postprandial insulin secretion, mimicking the normal insulin secretion and glucose metabolism of healthy individuals and thereby promoting a reduced risk of hypoglycemia [66, 67]. A randomized clinical trial demonstrated a similar efficacy between mitiglinide and nateglinide when used as a monotherapy in patients treated with diet and exercise in the three months leading up to trial [68].

Mitiglinide is rapidly absorbed and eliminated by the body [66] and metabolized in the kidneys and liver and generates metabolites with little of the secretory activity of insulin. The half-life of mitiglinide is 1.48 h [54], and it has been shown to prevent increases in oxidative stress and inflammation markers after meals in patients with diabetes mellitus because of the suppression of postprandial hyperglycemia promoted by this drug [69]. Because of its characteristics, mitiglinide is currently considered an ideal drug for the treatment of T2DM and is widely used in clinical practice [54].

5. Alpha-glucosidase inhibitors

The competitive inhibitors of alpha-glucosidase, such as acarbose, miglitol and voglibose, are administered orally and inhibit alpha-glucosidase, which is an enzyme that converts polysaccharides (e.g., amylase, maltase and sucrase) into monosaccharides, thus acting as an antagonist enzyme. Therefore, such inhibitors decrease the intestinal absorption of glucose, particularly postprandial absorption that modulates insulin secretion [70]. The slower rise in postprandial blood glucose concentrations is potentially beneficial in both type 1 and type 2 diabetes. In older patients with type 2 diabetes, acarbose may also increase insulin sensitivity [71]. These inhibitor lower the incidence of cardiovascular events, and they have no systemic absorption [72].

In addition, alpha-glucosidase is inhibited competitively, and its availability for oligosaccharides derived from the diet is reduced. Thus, there is a reduced formation of monosaccharides and less insulin is required for metabolism, which leads to a reduction of glucose (because it is not absorbed) as well as postprandial insulin-induced increases [73]. These effects reflect a significant decrease in glycated hemoglobin, which was observed in a meta-analysis of 41 trials of alpha-glucosidase inhibitor therapy (primarily acarbose trials) in which beneficial effects were observed (compared with placebo) on Hb_{A1c} (-0.77 percentage points), fasting, and postload glucose and postload insulin levels. These benefits are more evident in highly hyperglycemic patients. Hyperglycemia in patients with mild or moderate glycemic control is less common than in those using other oral antidiabetic agents. In such cases, competitive inhibitors of alpha-glucosidase can be used in combination with insulin or any other oral hypoglycemic agents [74-76].

The most frequent side effects of alpha-glucosidase inhibitors are observed at the intestinal level and include flatulence, diarrhea, abdominal pain and elevated transaminases [35, 77-79]

The occurrence of hypoglycemia and an increase in body weight are rare because the agent does not stimulate insulin release or hypersecretion. These effects are only observed when miglitol is combined with other therapies, and its use is contraindicated in cases of inflammatory bowel disease, pregnancy, lactation, and hepatic or renal impairment. In one prospective study of 893 patients treated with acarbose, only 16 to 20% were still taking the drug after one year, and half of the patients had stopped the drug during year two because of the side effects [80].

Recently, a mixed-treatment comparison (MTC) meta-analysis showed that there was no significant increase in hypoglycemia risk or body weight with alpha-glucosidase inhibitors [81].

5.1. Acarbose

Acarbose has a microbial origin and is structurally similar to natural oligosaccharides, with an affinity 104-105 times higher than drugs of the same class of alpha-glucosidases. With regard to its pharmacokinetic aspects, acarbose is poorly absorbed in the intestine (less than 2%). The products produced by bacterial enzymes cleave acarbose, yielding intermediate 4-methyl pyrogallol, which is conjugated and excreted as sulfates or glucuronidate [75].

Several trials have demonstrated the efficacy of acarbose in patients with type 2 diabetes [35, 82-85]. In one trial, 96 patients who were inadequately controlled by diet alone were randomly assigned to receive either glyburide or acarbose, and their Hb_{A1c} values and fasting blood glucose concentrations fell by a similar amount; the postprandial blood glucose concentrations, however, remained high in the glyburide group but fell in the acarbose group [83]. A second trial evaluated 354 patients treated with diet alone or diet plus a sulfonylurea, metformin or insulin. Compared with the placebo, the addition of acarbose in each of these groups reduced the mean postprandial blood glucose concentration and lowered the Hb_{A1c} values [35]. In general, acarbose has resulted in a greater improvement of Hb_{A1c} values than in fasting blood glucose concentrations, which is consistent with its predominant effect on postprandial hyperglycemia [85].

In a randomized, double-blind, placebo-controlled trial [82], satisfactory control of fasting and postprandial glucose occurred with acarbose in T2DM. In a multicenter, randomized, double-blind, placebo-controlled clinical trial [83] conducted for patients with T2DM who were subjected to a specific diet and use of insulin, the patients showed decreased levels of blood glucose and glycated hemoglobin as well as a reduced daily requirement for insulin.

In a systematic review of the literature, it was concluded that acarbose inhibits postprandial hyperglycemia by lowering insulin levels after a glucose overload. However, it presents no advantages with respect to corporal weight or lipid metabolism, and there are no statistically significant effects on mortality, morbidity and quality of life in patients with T2DM. Compared with the placebo, acarbose reduces Hb_{A1c}, fasting plasma glucose and postprandial glucose. Compared with sulfonylureas, it reduces glycemic control and has major adverse effects, particularly gastrointestinal effects [76]. Thus, treatment with acarbose might have a favorable effect on endothelial function in type 2 diabetes patients with ischemic heart disease [86-90]

5.2. Voglibose

Voglibose also has a microbial origin, and only 3-5% of the drug is absorbed at the intestinal level. It is a potent inhibitor of alpha-glucosidase, but it is weaker than acarbose in the inhibition of sucrase and has little effect on pancreatic alpha-amylase [75]. Furthermore, voglibose decreases the level of postprandial glucose with very low risk of hypoglycemia, but it is associated with frequent gastrointestinal side effects [91].

5.3. Miglitol

Miglitol has a synthetic origin and unique pharmacokinetic properties. It is absorbed rapidly through a transport mechanism in the jejunum that is close to the mechanism of glucose, and it is quantitatively excreted unchanged by the kidneys. Miglitol differs from acarbose because it does not inhibit alpha-amylase but rather inhibits intestinal isomaltase [75].

Based on studies in which miglitol was given alone or in combination with insulin or a sulfonylurea, the efficacy was similar to that of a placebo [92-95]. Miglitol is also effective when combined with metformin [96]. Thus, miglitol can be expected to suppress postprandial glucose more strongly than acarbose [97], so it should reduce the incidence of cardiovascular events [98].

6. Sulfonylureas

Another class of drugs used in the treatment of T2DM are the sulfonylureas chlorpropamide, acetohexamide, tolazamide and tolbutamide (first generation), glibenclamide, glipizide, gliclazide (second generation) and glimepiride (third generation). This class has long been established in the treatment of diabetes, and it was the first oral glucose-lowering medication to be introduced into clinical practice in the 1950s and has since been recognized as a first-line therapy as either a monotherapy or in combination [85, 99]. In the United Kingdom, sulfonylureas have been the second-line choice after metformin [100]. Furthermore, sulfonylureas are the drug of choice for type 2 diabetics who do not benefit exclusively from diet and exercise [101, 102].

Sulfonylureas usually lower blood glucose concentrations by approximately 20% and Hb_{A1c} by 1 to 2% [103, 104]. Recently, a systematic review of double-blind randomized control trials found that sulfonylurea monotherapy reduced Hb_{A1c} by an average of 1.5% (16 mmol/mol) compared with that of placebo groups [99, 105]. These drugs are most effective in patients whose weight is normal or slightly increased. In contrast, insulin should be used in patients (regardless of age) who are underweight, losing weight, or ketotic despite adequate caloric intake. Some of these latter patients may actually have type 1 diabetes, which can be confirmed by the presence of islet cell antibodies [106, 107].

Sulfonylureas act as insulin secretagogues and exert their main action on islet β cells, stimulating insulin secretion and thereby reducing the plasma glucose concentration. The mechanism of action involves binding of the drug to the subunit SUR1 of the ATP-sensitive potassium channels in the plasma membranes of β cells; these channels are then closed, which leads to a change in the membrane voltage, calcium influx and exocytosis of insulin granules [108-111]. The ATP-sensitive potassium channels are also present in other tissues but often contain different types of SUR subunits (e.g., SUR1 in β cells, SUR2A in heart cells, SUR2B in smooth muscle cells). The sensitivity of these different types of channels to sulfonylureas is variable [110].

The net effect of sulfonylureas is an increased responsiveness of β cells to both glucose and non-glucose secretagogues (such as amino acids), resulting in more insulin being released

at all blood glucose concentrations. Thus, sulfonylureas are useful only in patients with some β cell function. Sulfonylureas may also have extrapancreatic effects, which includes an increased tissue sensitivity to insulin; however, the clinical importance of these effects is minimal [101, 103].

The basal secretion and insulin secretory response to various stimuli are intensified in the early days of treatment with sulfonylureas. With long-term treatment, circulating insulin levels decline to levels that occurred before treatment; however, despite this reduction, the decreased plasma glucose levels are maintained. The mechanism for this response is still unknown but may be associated with reduced plasma glucose, which allows the circulating insulin to have more pronounced effects on their target tissues, as well as the impairment of insulin secretion by chronic hyperglycemia.

Sulfonylureas are well absorbed after oral administration by the gastrointestinal tract. However, the presence of food and hyperglycemia may reduce their absorption. The peak plasma concentrations occur within 2-4 hours, and the duration of the effect varies. All of these drugs bind tightly to plasma albumin and are involved in interactions with other drugs (e.g., salicylates and sulfonamides) such that there is competition for binding sites. All sulfonylureas are metabolized by the liver, and their active metabolites are mostly excreted in the urine; thus, their action is increased in elderly patients or those with renal or hepatic disease.

The choice of sulfonylurea is primarily dependent upon cost and availability because their efficacy is similar. However, because of the relatively high incidence of hypoglycemia in patients taking glyburide or chlorpropamide, shorter acting drugs should be used, especially in elderly patients [112]. In a patient who is not a candidate for metformin or cannot tolerate metformin as initial monotherapy, a shorter-duration sulfonylurea such as glipizide is suggested.

6.1. First-generation sulfonylureas

The first-generation sulfonylureas vary considerably in their half-lives and the extent of their metabolism. The acetohexamide half-life is short, but the drug is reduced to an active compound whose half-life is similar to that of tolazamide and tolbutamide (4 to 7 hours). If required, these drugs can be divided into daily doses. Chlorpropamide has a long half-life (24 to 48 hours) [113]

The action of chlorpropamide, acetohexamide, tolazamide and tolbutamide is long lasting, and there is substantial excretion in the urine. Therefore, these drugs can cause severe hypoglycemia in elderly patients who have experienced a progressive decline in glomerular filtration. These drugs cause flushing after alcohol consumption and exert similar effects to that of the diuretic hormone on the distal nephron, producing hyponatremia and water intoxication [113].

6.2. Second-generation sulfonylureas

The second-generation sulfonylureas (glibenclamide, glipizide and gliclazide) are more potent, but their hypoglycemic effects are not much improved, and they fail to control blood

glucose, which is commonly observed with tolbutamide. All of these drugs contain the sulfonylurea molecule, but different substitutions result in differences in pharmacokinetics and duration of action. Glibenclamide should be avoided in the elderly and patients with mild renal impairment because of the risk of hypoglycemia because several of its metabolites are excreted in the urine and are moderately active [113].

The sulfonylureas cross the placenta and stimulate insulin release by fetal β cells, causing severe hypoglycemia at birth. Consequently, their use is contraindicated during pregnancy, and gestational diabetes is treated by diets supplemented with insulin when required [113].

In general, sulfonylureas are well tolerated. The observed side effects are hematological, including hypoglycemia, leukopenia, agranulocytosis, thrombocytopenia, and hemolytic anemia, gastrointestinal, including nausea, vomiting, and cholestatic jaundice (rare), and allergic reactions. Sulfonylureas may also cause weight gain, and their binding to plasma proteins can be potentiated by other drugs used concomitantly, which may cause hypoglycemia. This condition is the most problematic adverse event and may be prolonged, which can have severe consequences in elderly patients, patients treated with multiple drugs and those with impaired renal function. Moreover, sulfonylureas stimulate appetite and can occasionally cause allergic rashes and bone marrow injury [113].

Sulfonylureas have structural characteristics that allow them to be given in much lower doses than the first-generation sulfonylureas. Nevertheless, the different sulfonylureas are equally effective in lowering blood glucose concentrations. There are, however, differences in absorption, metabolism and effective dose [114], which is partly caused by the formation of active metabolites [115]. These drugs also cause greater suppression of overnight hepatic glucose output, thereby lowering fasting blood glucose concentrations. These benefits may be counterbalanced by an increased risk of hypoglycemia [112].

6.3. Glimepiride

The US Food and Drug Administration (FDA) approved glimepiride in 1995 for the treatment of T2DM alone and in combination with metformin or insulin. It has prolonged action and lasts over 24 hours. Glimepiride has advantages with respect to its clinical and pharmacological profile, and it has also been shown to cause a low incidence of severe hypoglycemia compared to other representatives of its class [116, 117].

Regarding hypoglycemia, the findings observed in certain studies differ. In a systematic review and meta-analysis [118], glimepiride was found to cause increased hypoglycemia compared to other sulfonylureas and even more than other secretagogues. In other studies, the long-acting sulfonylureas, such as chlorpropamide and glibenclamide, were shown to have an increased likelihood of causing hypoglycemia [112, 119]. In a UK survey, the rate of diagnosis of hypoglycemia was higher for glibenclamide compared to other representatives of the same class [120].

With regard to weight gain, in the UK Prospective Diabetes Study [34], the mean weight change after 10 years of follow up ranged from a minimum of 1.7 kg as a result of glibenclamide use

to a maximum 2.6 kg with chlorpropamide use. Glimepiride was found to be neutral with respect to body weight, whereas other authors observed weight reduction [121, 122].

Sulfonylureas have different cross reactivities with cardiovascular ATP-dependent potassium channels. The closing of these channels by ischemic preconditioning can lead to cardiovascular mortality [123].

Several compounds increase the hypoglycemic effect of sulfonylureas, and several of these interactions are potentially important from a clinical standpoint. Non-steroidal anti-inflammatory agents (including azapropazone, phenylbutazone and salicylates), coumarin, certain uricosuric agents (e.g., sulfinpyrazone), alcohol, monoamine oxidase inhibitors, certain antibacterials (including sulfonamides, chloramphenicol, and trimethoprim) and certain antifungal agents (including miconazole and possibly fluconazole) produce severe hypoglycemia when administered with sulfonylureas. The probable basis for these interactions is the competition for metabolizing enzymes, but interference in plasma protein binding or excretion may also exert some effect. The agents that reduce the action of sulfonylureas include diuretics (thiazides and loop diuretics) and corticosteroids [113].

7. Anti-obesity medications

Obesity (body mass index (BMI) above 30 kg/m^2) is common in many diabetic patients, and it is important to highlight the rising prevalence of these two health conditions in the modern world [124]. Being obese or overweight produces important risk factors for type 2 diabetes and is associated with many serious health conditions, such as heart disorders and cancer, which lead to increased mortality, especially in individuals over 65. In patients previously diagnosed with type 2 diabetes, the presence of obesity can lead to a worsening of the metabolic disorders associated with diabetes, such as hyperglycemia, hypertension and hyperlipidemia [125, 126]. Thus, weight loss is required to improve glycemic control in the patient as well as to reduce the cardiovascular risk factors, which will likely reduce the risk of mortality in those individuals [127-129].

A systematic review published in 2011 [126] reported data from two clinical trials that showed a reduction of 30% to 50% in the incidence of diabetes in overweight and obese patients (with elevated plasma glucose levels) after behavioral interventions that lead to weight loss. However, the results arising from actions aimed at the prevention of obesity and changes in the obesogenic environment are often insufficient and produce insignificant weight loss that is usually regained over time. For these individuals, more invasive treatments are required to produce a sufficient weight reduction. Bariatric surgery has been a widely used intervention in obese patients because it promotes rapid and significant weight loss. However, the risks of surgery mean that this intervention is reserved for patients with morbid obesity. Thus, the FDA advises pharmacological intervention for patients with BMI ≥ 30 kg/m^2 (obese) or ≥ 27 kg/m2 (overweight) when in the presence of co-morbidities related to obesity [125, 130-132].

Numerous medications have been used for weight loss in recent decades; however, the occurrence of adverse side effects has restricted their current use [125]. In the 1990s, the drugs

fenfluramine and dexfenfluramine (sympathomimetic amines that promote appetite suppression) were withdrawn from the market because of the risk of heart damage. The European Medicines Agency (EMA) suggested the withdrawal of various anti-obesity drugs, such as diethylpropion (amfepramone), mazindol and phentermine (also sympathomimetic amines inhibiting appetite), in the 2000s because of the high risk of adverse events. In 2006, rimonabant (first selective blocker of endocannabinoid receptor subtype 1-CB1) became available in 56 countries; however, because of its adverse psychiatric events, this drug was never approved by the FDA and was withdrawn from the European market in 2009. Additionally, after clinical trials assessing the safety and tolerability of sibutramine (an appetite suppressant that acts as a selective inhibitor of the reuptake of norepinephrine and serotonin), the FDA considered the option to restrict access to this substance or withdraw it from the market, causing the suspension of marketing authorization in 2010 [130, 133].

From the drugs approved before 2012, several sympathomimetic amines are available. These include phentermine, diethylpropion, benzphetamine and phendimetrazine, which are approved for short-term weight management (≤ 12 weeks), and orlistat (a potent reversible inhibitor of gastric and pancreatic lipase capable of preventing the absorption of up to 30% of dietary fat), which is the only anti-obesity drug for long-term use [130, 134, 135]. In 2012, the FDA approved two new drugs for obesity control: lorcaserin (agonist of the serotonin receptor 5-HT2C) and extended release phentermine-topiramate (association between a sympathomimetic amine appetite suppressant and an anticonvulsant). The mechanism responsible for weight loss when using extended release phentermine-topiramate is believed to be the subsequent increase in activity of the neurotransmitter gamma-aminobutyric acid (GABA), although the exact association mechanism remains unclear. Both drugs were approved for long-term use [131, 136, 137].

Depression is a common side effect observed in patients with type 2 diabetes, which may be associated with a lack of glycemic control, increased risk of complications, lack of adherence to treatment and even the presence of obesity or overweightness [137, 138]. A meta-analysis in 2001 by Anderson et al. showed that the prevalence of depression was twice as high in individuals with T2DM than in those without this health condition. Thus, reducing the incidence of depression and improving the quality of life of diabetic patients, especially those who are also obese, are highly relevant clinical objectives [139-141]. The treatment of depression in diabetics is usually accomplished by the use of serotonin reuptake inhibitors, such as fluoxetine and sertraline. These drugs not only act on depression but also promote weight loss, which is highly desired in obese or overweight diabetics [68, 142].

8. SGLT2 inhibitors

8.1. Dapagliflozin

Dapagliflozin was the first hypoglycemic agent of the new class of selective reversible inhibitors of sodium-glucose cotransporter 2 (SGLT2) approved in the US (April 2012) and demonstrates a new mechanism of action independent of insulin. This drug is recommended

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in adults aged 18 years or older with type 2 diabetes, both as a monotherapy and as a combination therapy with other hypoglycemic drugs, including insulin when diet and exercise does not provide adequate glycemic control [143-145].

The hypoglycemic effect occurs by reducing the reabsorption of glucose from the renal proximal tubule, which leads to increased urinary excretion of glucose with an associated loss of calories [143, 144]. On average, a daily dose of 10 mg dapagliflozin increases the amount of glucose excreted in the urine of a patient with type 2 diabetes to 50-80 g/day. This effect is observed with the first dose, and with chronic treatment, this increased excretion of glucose can be maintained for at least two years [146, 147].

In patients with type 2 diabetes, urinary loss of glucose works through a mechanism independent of insulin secretion and action [148-153] and has the potential to improve glycemic control, including control of Hb_{A1c}, fasting plasma glucose and postprandial glucose.

The selectivity of dapagliflozin for SGLT2 is 1000-3000 times greater than for SGLT1 [154].

Dapagliflozin is rapidly and extensively absorbed following oral administration. The oral bioavailability of a 10 mg dose is ≥ 75% and may be administered with or without food. It is extensively metabolized to inactive conjugates, predominantly dapagliflozin 3-*O*-glucuronide, which is then eliminated via the kidneys [146, 154].

Dapagliflozin's effectiveness is dependent on renal function and therefore should not be used by patients with moderate to severe renal impairment; dose adjustment is necessary for patients with mild renal failure or moderate hepatic impairment. Moreover, dapagliflozin should not be used in patients with severe hepatic impairment because exposure to dapagliflozin can be increased.

Interactions between dapagliflozin and other agents routinely used in the control of diabetes mellitus, including sulfonylureas, statins, warfarin and digoxin, were observed [154].

Dapagliflozin was generally well tolerated in clinical trials lasting 1 or 2 years and in studies lasting approximately 2 years [146]. Polyuria, nocturia and thirst may be experienced by some patients, and the increased excretion of glucose causes osmotic diuresis, which is similar to what is observed in patients with uncontrolled diabetes. The additional fluid loss of 300-400 ml/day is well tolerated by most patients [149, 155].

Genital infections are common in patients receiving dapagliflozin because glycosuria provides a favorable environment for the growth of microorganisms [146, 149, 155].

Dapagliflozin is recommended for patients with T2DM in the following situations [154]:

1. Monotherapy as an adjunct to diet and exercise when metformin is not tolerated;
2. Combined therapy
3. with metformin, diet and exercise, to improve glycemic control in patients when these measures alone do not achieve adequate glycemic control and there is little prospect of therapeutic response to metformin (e.g., high Hb_{A1c} levels);

4. with a sulfonylurea when sulfonylureas alone with diet and exercise do not provide adequate glycemic control; and

5. with insulin (alone, with metformin or a sulfonylurea or both) when existing therapy along with diet and exercise do not provide adequate glycemic control;

A number of other SGLT2 inhibitors are under investigation, including empagliflozin, canagliflozin and ipragliflozin. In addition, a non-selective SGLT inhibitor (LX4211) is under development. It is likely that these and other agents that share similar pharmacodynamic properties may become available in the coming years [146].

9. Insulins

In 1921, insulin was introduced as a therapeutic drug, which improved the quality and life expectancy of diabetics. The first available commercial insulin preparations corrected acute diabetic decompensation but were inefficient for chronic use because their duration was too short. Thus, diabetics were required to take four to five injections daily to achieve good metabolic control. Such short-acting insulin was the only commercially available type in 1935. Prolonging the action of insulin to over 24 hours could achieve the aim of decreasing the amount of daily injections, and it was achieved by incorporating certain substances, such as oily solutions, heavy metals (zinc) and protein (protamine). In 1950, by changing the concentration of protamine and decreasing the amount of zinc, the intermediate insulin called isophane or NPH ("Neutral Protamine Hagedorn" in honor of the scientist) became available. There were still more changes in the formula that affected the time of action, and in 1954, the family of insulins slow, semi-slow, or ultra-slow containing zinc instead of protamine was produced [156, 157].

The use of insulin is essential in the treatment of type 1 diabetes mellitus. In T2DM, it is reserved for patients with severe hyperglycemia with ketonemia or ketonuria, newly diagnosed diabetics or those who do not respond to treatment with diet, exercise, oral hypoglycemic agents and the anti-hyperglycemic action of insulin sensitizers [158].

A milestone in diabetes therapy occurred with the Diabetes Control and Complication Trial (DCCT), which showed that blood glucose levels close to normal drastically reduced or even prevented the complications of diabetes when the carrier of the disease was subjected to intensive insulin treatment and follow-up with a team of diabetes educators. According to the DCCT, to achieve this control, one proposal is to replace conventional insulin treatments (one or two daily applications of insulin) with an intensive treatment of up to four applications per day [159].

Currently, attempts to achieve good metabolic control in patients with diabetes include treatment with exogenous insulin, which is an effective therapy option in cases of partial and/or total deficiency of insulin secretion by the pancreas. It is estimated that 20-25% of all patients

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with diabetes are treated with insulin, and 5-10% of these patients are type 1 (who need this hormone to survive) and 15% are type 2 (who show severe insulin deficiency) [157].

Commercial insulin is a protein hormone with two linked chains of amino acids that cannot be administered orally because it is degraded by digestive and intestinal enzymes. Most commercial insulin is manufactured from bovine and porcine pancreases, which are similar to the human pancreas. Bovine and human insulin differ in three amino acids, whereas porcine insulin differs in one amino acid (amino acid thirty). Chemically synthesized insulin is also produced by recombinant DNA techniques that use bacterial cells or other tissues that are free from impurities and have a minor antigenic action [160, 161].

The pharmacokinetics of insulin varies according to its type and kind, injection technique, presence of insulin antibodies, site of injection and the individual [162].

Commercial preparations of insulin are classified according to duration as either short, intermediate or long acting, and the species of origin is also a classifier, with insulin derived from human, porcine, bovine and or porcine bovine mixtures. Because of differences in the amino acid sequences, the bovine and porcine insulins have different physicochemical properties to human insulin. Human insulin has become widely available following the advent and development of recombinant DNA techniques [163]. These techniques have led to different formulations of insulin that differ according to recombinant DNA production techniques, amino acid sequences, concentrations, solubility and time of onset and duration of biological action. However, insulin produced through recombinant DNA technology are more soluble in aqueous solutions. Currently, the commercially available forms are supplied at neutral pH, resulting in improved stability, which is essential for storage over several days at room temperature [164].

The long-acting analogues such as glargine and detemir appeared on the market in 2000 and 2004, respectively [165], and they show a relatively stable profile of action over time [166]. In January 2013, the European Commission authorized the introduction of a new generation of ultra-long insulin analogues. Degludec insulin is an ultra-long acting basal insulin analogue [167].

9.1. Short or ultra-rapid acting insulin

This group of insulins includes regular, lispro, aspart and glulisine analogues.

Regular insulin is usually administered subcutaneously and often in combination with intermediate-acting or long-lasting insulin. Special buffers are used so that a pump is not required to prevent crystallization because of its slow infusion. Monomers of this insulin present as hexamers that reduce the absorption rate. Normally, regular insulin is recommended for the treatment of diabetic ketoacidosis, and it is associated with human intermediate-acting insulin or basal analogs taken before meals [168]. This insulin should be administered 30-45 minutes before meals to reduce peak postprandial glycemia, and its action lasts between 2 and 4 hours, which contributes to postprandial hyperglycemia and

hypoglycemia in the period between meals because regular insulin will peak after food has been metabolized [169].

Insulin lispro is a human insulin analog developed through genetic engineering by reversing the amino acids proline and lysine at positions 28 and 29 of the β chain, which results in the insulin sequence Lys (B28) Pro (B29). This insulin in its pharmaceutical preparation with phenol and zinc form stable hexamers [168], has a reduced tendency to self-aggregate at the site of subcutaneous injection, is absorbed more rapidly than regular human insulin, and mimics the physiological profile of insulin in response to a meal. In addition, its onset of action is between 5 and 15 minutes and duration of action is 1-2 hours [170]. The use of these analogues requires an additional dose in the afternoon to compensate for the hyperglycemia that results from an afternoon snack. There is evidence that insulin lispro reduces postprandial hyperglycemic peaks and the risk of hypoglycemia compared to regular insulin, especially at night [168, 171].

In aspart insulin, one proline amino acid is replaced by aspartic acid, which is negatively charged, at position 28 of the β chain, producing electrical repulsion between the insulin molecules and reducing their self-association tendency; in vials or cartridges, it occurs as hexamers, but in subcutaneous tissue, there is rapid dissociation to dimers and monomers, which ensures its rapid absorption and onset of action between 5 and 15 minutes and duration of action of 1 to 2 hours[168].

Insulin glulisine is another ultra-rapid insulin analogue obtained by the exchange of asparagine for lysine at position 3 of the β chain and lysine for glutamic acid at position 29 of the same chain. Thus far, there have been few studies with glulisine insulin, which appears to be similar to lispro and aspart in efficacy and hypoglycemic events. Because of its faster absorption, its administration should be performed only 5-10 minutes before meals to provide greater flexibility for the patient and thereby improve their quality of life. Its shorter half-life reduces the need to eat food 2-3 hours after its administration, which is necessary with regular insulin, whose longer half-life causes postprandial hypoglycemia [172].

A recent direct and indirect meta-analysis published by Sanches et al. (2013) for glycated hemoglobin reduction outcomes compared rapid action insulin (aspart, glulisine and lispro) with human insulin (regular), and the direct meta-analysis only showed a statistically significant difference for aspart, favoring the insulin analog. However, the results of indirect meta-analyses of Hb_{A1c} reduction outcomes showed that the result of rapid-acting insulin are consistent and the difference between them is not clinically significant. The ranking suggests that the probability of selecting the short-acting insulin brings the following provision: the first choice should be regular followed by glulisine, lispro and finally aspart. No significant differences were found in the comparison of tolerability outcomes in the rapid-acting insulin (aspart and lispro) and human insulin (regular) [173].

Recent studies have attempted to alter the pharmacokinetics of fast acting insulin analogues that are associated with recombinant human hyaluronidase, and they revealed that absorption was accelerated two-fold during the first half hour of exposure, which resulted in an onset of action between 13 and 25 minutes faster and a shorter duration of effect (40 to 49 minutes).

The ultra-rapid action arising from this association may be beneficial in furthering the control of postprandial blood glucose, and administering insulin lispro and hyaluronidase immediately before meals in patients with type 1 or 2 diabetes may be beneficial. Studies are being conducted for the commercial production of HUMALOG ® (Eli Lilly Nederland B.V) as part of an intensive basal-bolus insulin treatment for these patients [174].

9.2. Intermediate insulins

NPH insulin was released in 1946, and it is an insulin suspension in a zinc complex and protamine phosphate buffer. Its dosage is usually once a day before breakfast or twice a day. It has an absorption peak approximately 4-6 hours after subcutaneous administration, which is followed by a steady decline in plasma insulin concentrations [175].

The major disadvantages of NPH are the wide daily variations in the timing and duration of peaks among and between individuals, which, when compared to the timing and duration of long-acting analogs, may result in non-optimal metabolic control and an increased risk for nocturnal hypoglycemia. [172].

With respect to better glycemic control and safety when comparing the use of NPH with long-term insulin analogues, a meta-analysis published in 2013 showed that in type 2 diabetic patients, glycemic control does not seem to differ among different classes, although there is evidence for a possible reduced risk of nocturnal hypoglycemia.

Other information found in the study was that only detemir (and not glargine) may be associated with less of a weight gain than is associated with NPH [176]. In an indirect meta-analysis of long-term insulin, the results of reducing Hb_{A1c} are consistent with data from direct comparison meta-analyses and allowed a ranking of probability choice of insulins to improve the reduction of Hb_{A1c} as follows: NPH, glargine and detemir [173, 177].

9.3. Basal insulins

Glargine and detemir insulin analogs represent groups referred to as long-term or basal [168]. Detemir is produced by means of recombinant DNA technology with expression in *Saccharomyces cerevisiae* followed by chemical modification [178]. A fatty acid (myristic acid) is attached to the lysine at position 29, and it binds to circulating albumin, forming a complex that dissociates slowly, thereby prolonging its action time. Detemir is soluble at neutral pH but cannot be mixed with the rapid analogs. Detemir has shown potential benefits in body weight control, with weight loss or decreased weight gain in adults and in children and adolescents [179].

Glargine is synthesized from changes in the amino acid chain of human insulin through a substitution of asparagine by glycine at position A21 and the addition of two arginines at position B30. These modifications result in a unique pattern of release from the injection site, meaning that this analog precipitates in the subcutaneous tissue, allowing a gradual absorption into the bloodstream [180].

Basal insulin has been developed to promote basal levels of insulin over 24 hours and can be administered once a day or at bedtime. When comparing conventional long-acting insulin with glargine insulin, the insulin analog is observed to have a constant concentration profile without prominent peaks [181]. In addition, the onset is between 1 and 2 hours, plateau of biological action is between 4 and 6 hours and termination of effect is between 20 and 24 hours. Because of its slightly acidic pH, glargine cannot be mixed with other insulins in the same syringe; therefore, children may sometimes complain of a burning sensation at the application site [168]. The timing of administration of glargine appears to have no impact on its efficacy for glycemic control, but the administration should occur at approximately the same time each day so that its effectiveness as an insulin is maintained without peak action. If a dose is missed, 50% of the daily insulin will be missing that day [172].

In a direct meta-analysis comparing the insulin analogues (glargine and detemir) to NPH insulin in reducing glycated hemoglobin, the results were statistically significant and favored the twice-daily administration of detemir alone. The safety and tolerability results also showed minor differences between the insulin analogues and NPH insulin [173].

The insulin degludec belongs to a new class of insulin analogues and has a unique absorption mechanism that allows for an ultra-slow and stable pharmacokinetic profile. Its structure differs from human insulin at the β chain termination with removal of threonine at position B30 and a 16-carbon fatty acid attached to lysine at B29 by glutamic acid. This change allows for the formation of a deposit of soluble multi-hexamers, which accumulate in the subcutaneous tissue and have a slow release because of the dissociation of zinc ions; therefore, degludec insulin monomers are circulated in a slow and sustained fashion. In clinical trials, it was observed that the pharmacokinetic variations are four times smaller than in the other long-acting insulin analogues. Studies show that this insulin is related to a lower risk of nocturnal hypoglycemia, and because of these characteristics, administration can occur at intervals of up to 40 hours [182, 183].

New insulins, such as U300 and LY2605541 insulins, are still under investigation. Insulin glargine U300 is a new formulation containing glargine in a 300 U/mL concentration (the usual concentration is 100 U/mL). This change alters the pharmacokinetic and pharmacodynamic properties of glargine. For subcutaneous injections, a compact deposit of U300 is administered with a smaller deposit surface, and this produces a more gradual and prolonged release than conventional glargine; therefore, its pharmacokinetic profile is more regular and shows plasma concentrations even beyond 24 hours [184].

Another new insulin, LY2605541, is a long-acting insulin that is a modification of lispro insulin with a 20 kDa polyethylene glycol and half of lysine B28 through covalent urethane, which increases the hydrodynamic size of the insulin complex. This surface provides a greater delay in absorption and reduces the clearance, resulting in a prolongation of its action. This modified insulin has a low affinity for binding to the growth factor receptors linked to insulin, which reduces its mitogenic potential compared to human insulin. Its average life is 24-45 hours, and the duration of action may exceed 36 hours. Animal studies suggest selective action on hepatic metabolism [184].

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9.4. Inhalable insulin

The benefit of injectable insulin is often limited because of the difficulty of convincing the patient to adhere to proper treatment, which is related to the need for multiple injections to ensure adequate glycemic control [185].

To alleviate this discomfort, the first inhalable insulin (Exubera®, Pfizer/Nektar) was approved in the U.S. in January 2006. Exubera® consists of a dry powder formulation containing 1 to 3 g of human insulin administered via a single inhaler lung [186]. The technology used in this product was the development of an inhaler for polyethylene glycol in a dry powder that releases the equivalent to 3 UI and 8 UI of short-acting insulin subcutaneously [187]. Exubera® has demonstrated efficacy and a low risk of hypoglycemia; however, there was a poor acceptance by the prescriber and patient. In April 2008, clinical trials showed the first case of cancer, and there were six subsequent cases of lung cancer and a case of primary malignant lung tumor in a patient who had a history of smoking. Other important aspects are coughing, decline of lung function, and increase of anti-insulin antibodies [188]. These facts led the manufacturer to withdraw Exubera® from the market.

The insulin AERx was developed by the Aradigm Corporation and Novo Nordisk. This system generates aerosol droplets from liquid insulin, and the devices guide the user to inhale the insulin. Moreover, it offers the ability to download data on the use of insulin, such as the frequency of inhalation, which can allow for the monitoring of treatment, which is important because of the experience with Exubera® [189].

AFREZZA™ (insulin Technosphere®) overcomes some of the barriers that contributed to the withdrawal of Exubera® from the market. Studies have shown that Technosphere® is a unique formulation of ultra-rapid insulin with a relatively short duration that effectively improves glycemic control without contributing to an increase in weight gain or hypoglycemia compared to other prandial insulins. Additionally, Technosphere® insulin has shown a favorable safety and tolerability profile in clinical studies to date [190]. Technosphere® insulin (TI) combines the post-dried recombinant human insulin (Mannkind Corp.) with the MedTone® Inhaler (Pharmaceutical Discovery Corp.) [191, 192.]. Recently the FDA approved this insulin; however, a continuation of the studies is required in the post-marketing period.

10. Conclusion

Despite the variety of drugs currently available for the treatment of type 2 diabetes, there was no observed decrease in the number of patients who have inadequate glycemic control keeps the last 10 years. This occurs for a variety of reasons, such as non-adherence to treatment, inappropriate prescribing of medication, lack of efficacy of medicine, among other reasons.

The search of glycemic control in patients with T2DM is still a challenge for patients and health professionals. Importantly, the success of drug treatment also depends on the association with non-pharmacological measures such as healthy diet and exercise.

Author details

Roberto Pontarolo[1], Andréia Cristina Conegero Sanches[2], Astrid Wiens[1], Cássio Marques Perlin[1], Fernanda Stumpf Tonin[1], Helena Hiemisch Lobo Borba[1], Luana Lenzi[1] and Suelem Tavares da Silva Penteado[1]

*Address all correspondence to: pontarolo@ufpr.br

1 Department of Pharmacy, Federal University of Paraná, Curitiba, Paraná, Brazil

2 Department of Medical and Pharmaceutical Sciences, State University of West of Paraná, Cascavel, Paraná, Brazil

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