A mini review of pharmacotherapy of type 2 diabetes – drugs and mechanisms

Resumo

Diabetes mellitus (DM2) é uma doença crônica que origina de inúmeros mecanismos patogênicos, todos eles, em hiperglycemia. Esta doença é uma das principais causas de morbidade e mortalidade em todo o mundo. Portanto, estratégias eficazes de prevenção e tratamento para o DM2 são necessárias. O objetivo desta revisão foi resumir a farmacoterapia para pacientes com DM2 discutindo sua fisiopatologia, as classes terapêuticas utilizadas nas estratégias de tratamento, bem como os mecanismos de ação de cada fármaco. Uma revisão de literatura foi realizada por meio de busca nos bancos de dados Google Scholar, PubMed e Science Direct usando os termos de busca: diabetes mellitus tipo 2, insulina, AMPK, antidiabéticos, incretinas, SGLT2, e biguanidas abrangendo estudos até 2022. A revisão identificou e incluiu estudos qualitativos, artigos de pesquisa originais e ensaios clínicos randomizados. Os resultados deste estudo são divididos em drogas que aumentam a sensibilidade à insulina (por exemplo, biguanidas, e thiazolidinediones), secretagogues (e.g., sulfonylureas, and meglitinides or glinides), incretina mimetics drugs (e.g., GLP-1 receptor agonists, and DPP-4 inhibitors), drugs that cause glycosuria (e.g., SGLT2 inhibitors), drugs that prevent glucose absorption (e.g., α-glucosidase inhibitor), and insulin. This allows the readers to understand each process while keeping the paper concise.

Keywords: Diabetes Mellitus; Glycemic control; Hypoglycemic agents.

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para la DM2. El objetivo de esta revisión fue resumir la farmacoterapia para pacientes con DM2, discutiendo su fisiopatología, las clases terapéuticas utilizadas en las estrategias de tratamiento, así como los mecanismos de acción de cada fármaco. Se realizó una revisión de la literatura buscando en las bases de datos de Google Scholar, PubMed y ScienceDirect utilizando los términos de búsqueda: diabetes mellitus tipo 2, insulina, AMPK, antidiabéticos, incretinas, SGLT2 y biguanidas que abarcan estudios hasta 2022. La revisión identificó e incluyó estudios cualitativos, originales artículos de investigación y ensayos controlados aleatorios. Los resultados de este estudio se dividen en fármacos que aumentan la sensibilidad a la insulina (p. ej., biguanidas y tiazolidinedionas), secretagogos (p. ej., sulfonilureas y meglitinidas o glinidas), fármacos miméticos de incretina (p. ej., agonistas e inhibidores del receptor GLP-1) de la DPP-4), fármacos que causan glucosuria (p. ej., inhibidores de SGLT2), fármacos que impiden la absorción de glucosa (p. ej., inhibidor de α-glucosidasa) e insulina. Esto permite a los lectores comprender cada proceso, manteniendo el artículo conciso.

**Palabras clave:** Diabetes Mellitus; Control glucémico; Hipoglucemiantes.

1. **Introduction**

1.1 **Physiological control of glycemia**

The regulation of blood glucose, or glycemia, involves the integration of several important organs, including the gastrointestinal tract, the brain, adipose tissue, the liver, skeletal muscle, and, most importantly, the pancreas – a mixed gland with exocrine (production of enzymes) and endocrine (hormone production) functions (Lin, et al., 2021). The β cells of the pancreatic islets produce insulin, while the α cells produce glucagon (Deng & Thorn, 2022). Insulin secretion is a tightly regulated process aimed at maintaining stable blood glucose concentrations in both fasting and prandial states (Saltiel, et al., 2021).

The molecular events that control glucose-stimulated insulin secretion begin with the transport of glucose into the β cell via the GLUT transporter (e.g., GLUT 2) present in the cell membrane (Knudsen, et al., 2020). On the other hand, the GLUT4 transporter is translocated from intracellular vesicles to the cell surface, where it responds to insulin by facilitating glucose uptake, mainly in skeletal muscle and adipose tissue (Klip, et al., 2019; Sylow, et al., 2021). Insulin is an anabolic hormone that stimulates glycogenesis (glycogen synthesis) and protein synthesis, increasing glucose uptake, in addition to acting by inhibiting the catabolism of these compounds (Saltiel, et al., 2021). Thus, it is crucial that glycemic homeostasis be regulated, as failures in these mechanisms can lead to serious metabolic disorders, including diabetes (Fralick, et al., 2022). Figure 1 describes the main mechanisms that regulate glycemic levels and the pharmacological targets for the treatment of type 2 diabetes.
Figure 1. Pharmacologic mechanisms of Antidiabetic Drugs.

1) GLP-1 receptor agonists enhance the effects of incretin hormones and are resistant to degradation by DPP-4. DPP-4 inhibitor drugs increase the impact of endogenous incretins. 2) Sulfonylureas and Glinides are secretagogue drugs that stimulate the pancreas to secrete insulin by inhibiting KATP channels in pancreatic β cells. 3) Thiazolidinediones are PPAR-γ receptor agonists that increase glucose uptake in muscle. 4) Biguanides are drugs that act by activating the AMPK pathway, improving insulin sensitivity in peripheral tissues. 5) Insulin stimulates GLUT4 translocation and increases protein synthesis and glucose transport. 6) Thiazolidinediones and Biguanides increase insulin sensitization and decrease glucose levels. Abbreviations: GLUT-4, glucose transporter-4; GLP-1, glucagon-like peptide-1; DPP4, dipeptidyl peptidase; AMPK, adenosine monophosphate-activated protein kinase. Source: Authors.

1.2 Pathophysiology of type 2 Diabetes Mellitus (T2DM)

Diabetes mellitus (DM) is classified as type 1 (T1DM) – which is concentrated in 5 to 10% of the total number of people with the disease – or type 2 diabetes mellitus (T2DM), which affects 90% of people with this disease (Fralick, et al., 2022). In this sense, the clinical condition for the diagnosis of DM is based on laboratory evidence of random hyperglycemia greater than 200 milligrams per deciliter (mg/dL), glycated hemoglobin A1c (HbA1c) greater than or equal to 6.5%, and the presence of classic symptoms of the disease (e.g., polyuria, polydipsia, etc.) (Inzucchi, et al., 2015). In T2DM, the main defect that leads to hyperglycemia is resistance to insulin action and the progressive loss of pancreatic β cell functionality, which stop producing insulin over time (Svitlana, et al., 2021).

2. Methodology

A literature review was conducted to identify articles related to the pharmacotherapy of type 2 diabetes mellitus, and available on Google Scholar (https://scholar.google.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), and Science Direct (https://www.sciencedirect.com/). Inclusion criteria were published articles written in English, including qualitative, original research articles, and randomized controlled trial designs covering studies up to 2022. The following keywords were used: type 2 diabetes mellitus, insulin, AMPK, antidiabetic drugs, incretin, SGLT2, and biguanides. Exclusion criteria were articles not accessible through university services, articles in another language than English, review articles, and articles previously found in another database. Nonetheless, references in found studies were checked. Table 1 shows the results of the search for articles
in the three databases.

### Table 1 - Search results from articles in databases.

<table>
<thead>
<tr>
<th>Database</th>
<th>Number of articles found up to 2022</th>
<th>Number of articles added to the review</th>
</tr>
</thead>
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<td><strong>28</strong></td>
</tr>
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Source: Authors.

3. Reviews

3.1 Medications

The treatment of T2DM can vary greatly depending on the individual clinical presentations of patients (Inzucchi, et al., 2015; Fralick, et al., 2022). In general, treatment with mono or dual therapy is initiated. In step 2, a third antidiabetic drug is added. In step 3, usually when the patient does not respond well to hypoglycemic drugs, nocturnal basal insulin (e.g., NPH) is added to block hepatic glucose production. However, in step 4, only full insulinization is performed with basal and prandial insulins, since the pancreatic β cells stop producing the hormone (Verberne & Mussa, 2022). It is important to mention that throughout all treatment stages, lifestyle changes are recommended, such as healthy eating and physical exercise (Knudsen, et al., 2020).

3.1.1 Drugs that increase insulin sensitivity

These drugs reduce hepatic gluconeogenesis by improving insulin sensitivity in peripheral tissues. Examples are biguanides (e.g., metformin) and thiazolidinediones.

i) Biguanides

Metformin is a very safe and well-tolerated drug in the treatment of T2DM. However, it is contraindicated in patients with renal impairment (glomerular filtration < 30 mL/min) or in any situation at risk of hyperlactatemia (such as decompensated liver failure, sepsis, or hypotension) due to the risks of lactic acidosis (González-González, et al., 2022).

**Mechanism of Action.** Metformin acts by activating the adenosine monophosphate-activated protein kinase (AMPK) enzyme, which increases glucose uptake in peripheral tissues, decreasing blood glucose (Hasanvand, 2022). AMPK is an enzyme involved in the metabolism of lipids and carbohydrates. When activated, the enzyme increases glucose uptake and decreases cholesterol and fatty acid synthesis, reducing the clinical signs of metabolic syndrome (Aslam & Ladilov, 2022).

ii) Thiazolidinediones (TZDS)

TZDs (e.g., pioglitazone) are PPAR-y receptor agonists that increase glucose uptake in muscle. However, as they promote greater retention of sodium and water, these drugs are contraindicated for patients with heart failure (Zhang, et al., 2021). In addition, they cause edema and promote weight gain (Yau, et al., 2013). PPAR-y are nuclear receptors for steroids and thyroid hormones, widely expressed in muscle, adipose tissue, and the liver (Chandra, et al., 2022). When these receptors are activated, they modulate the expression of genes involved in lipid and glucose metabolism and in the transduction of insulin signals, increasing the expression of the glucose transporter (GLUT-2 and GLUT-4) and, consequently, increasing glucose uptake (Klip, et al, 2019; Irudayaraj, et al., 2022).
3.1.2 Drugs that stimulate insulin secretion (secretagogues)

i) Sulfonylureas (SUs)

Secretagogues stimulate the pancreas to secrete insulin. Examples include Sulphonylureas and Glinides (Tomlinson, et al., 2022). Among the sulfonylureas, are the 1st generation agents, such as Chlorpropamide (rarely used), and the 2nd generation agents – which are pharmacologically more potent – such as Glibenclamide, Gliclazide, Glimepiride, and Glipizide (Lavania, 2019; Scheen, et al., 2021).

Mechanism of Action. After being internalized in the pancreatic cell, glucose is metabolized and there is a change in the ADP/ATP ratio. Elevated ATP levels inhibit ATP-sensitive K+ channels (KATP channel), leading to cell membrane depolarization. This leads to the opening of voltage gated Ca2+ channels and an increase in intracellular Ca2+, resulting in the release of insulin from storage vesicles by exocytosis (Shyng, 2022). When released, insulin is carried by the systemic circulation where it will act on target organs that have specific receptors for insulin (e.g., liver, muscle, and adipose tissue) (Haq, et al., 2021).

ii) Meglitinides or Glinides

Among the Glinides, the most prescribed are Repaglinide and Nateglinide. These drugs act by inhibiting KATP channels in pancreatic β cells, leading to membrane depolarization and increasing intracellular Ca2+. As a result, insulin secretion occurs independently of glycemic levels, thus increasing the risk of hypoglycemia (Wei, et al., 2018; Svitlana, et al., 2021). In addition, the main undesirable effects of these drugs are weight gain (Haq, et al., 2021).

3.1.3 Incretin mimetics drugs

These drugs increase the effects of incretin hormones by facilitating glucose uptake. For example, there are dipeptidyl peptidase (DPP-4) inhibitors (orally) and glucagon-like peptide-1 (GLP-1) receptor agonists (injected) (Inzucchi, et al., 2015; Haq, et al., 2021).

i) GLP-1 Receptor Agonists

During food uptake in healthy individuals, ingested carbohydrates (e.g., glucose, fructose, and galactose) are metabolized to glucose and enter the systemic circulation. Concomitantly, incretins (GLP-1 and glucose-dependent insulinotropic polypeptide - GIP) are released by the gastrointestinal tract (GIT) (Haq, et al., 2021). These peptides stimulate insulin release before glucose reaches pancreatic islet β cells. In the treatment of diabetes, drugs are used to potentiate these mechanisms. GLP-1 analogues such as Liraglutide, Exenatide, and Lixisenatide, have been approved for daily use, while Semaglutide and Dulaglutide have been approved for weekly use (Lingvay, et al., 2022). The latter agents increase adherence to treatment.

Mechanism of Action. GLP-1 receptor agonists act by inducing insulin secretion and decreasing glucagon release. These drugs resemble GLP-1 itself, with the advantage of being resistant to degradation by DPP-4. Furthermore, these drugs decrease gastric emptying, do not cause hypoglycemia, and reduce appetite, decreasing weight gain (Wharton, et al., 2021).

ii) DPP-4 inhibitors

The effects of incretins are interrupted by the enzyme dipeptidyl peptidase-4 (DPP-4). Therefore, there are DPP-4 inhibitor drugs that increase endogenous incretins, thus controlling glycaemic levels. Among the DPP-4 inhibitors are Linagliptin, Sitagliptin, Saxagliptin, Vildagliptin, and Alogliptin (Min, et al., 2018). These drugs are safer and do not cause
hypoglycemia, as they act by facilitating the release of insulin only in response to high blood glucose levels (e.g., after a meal) (Haq et al., 2021). Therefore, they are recommended for the treatment of elderly patients, including individuals with kidney disease.

3.1.4 Drugs that cause glycosuria

i) Sodium glucose co-transporter 2 (SGLT2) inhibitors

Drugs such as Empagliflozin, Dapagliflozin, and Canagliflozin have extra glycemic benefits, such as decreased cardiovascular or renal risk in patients who have these established diseases (Haq, et al., 2021; Ku, et al., 2021).

Mechanism of Action. These drugs act by inhibiting sodium-glucose cotransporter 2 (SGLT-2), decreasing renal glucose reabsorption, and consequently increasing its urinary excretion, inducing the reduction of glycemia regardless of endogenous secretion or insulin action (Svitlana, et al., 2021). Furthermore, SGLT2 inhibitors (e.g., Empagliflozin) improve endothelial function by decreasing oxidative stress in diabetic patients (Mone, et al., 2022). By promoting glycosuria, these drugs cause negative energy balance leading to weight loss and increasing the risk of ketoacidosis in diabetic patients compared with DPP-4 inhibitors and sulfonylureas (Dawwas, et al., 2022). However, they may increase the risk of urinary tract infections (e.g., candidiasis) (Alexander, et al., 2022).

3.1.5 Drugs that prevent glucose absorption

i) α-glucosidase inhibitor

α-glucosidase are enzymes present in the brush border of the intestine that facilitate the absorption of carbohydrates, increasing postprandial blood glucose, and alpha-glucosidase inhibitors (AGIs) inhibit this very mechanism (Min, et al., 2018). Drugs in this group, such as Acarbose, control postprandial hyperglycemia. Importantly, they do not cause hypoglycemia or weight gain because they do not increase insulin secretion (Hanefeld, et al., 2004). However, they cause adverse GI effects (e.g., flatulence, bloating) and are not tolerated in continued use (Zhang, et al., 2021). Another α-glucosidase inhibitor is Miglitol, which is systemically absorbed and excreted by the kidneys (Haq, et al., 2021).

3.1.6 Insulin

Insulin activates the pathways and processes involved in glucose uptake and storage in addition to inhibiting the pathways involved in its degradation. These effects are mediated by the activation of tyrosine kinase receptors located on the plasma membrane, resulting in tyrosine autophosphorylation mediating the effects of insulin in various organs (Pullen, et al., 1976). In the liver, insulin inhibits glycogenolysis (breakdown of glycogen to form glucose) and increases the storage of glucose in the form of glycogen (Saltiel, et al., 2021). In muscle, insulin increases protein synthesis and glucose transport, as well as increasing triglyceride storage and inhibits intracellular lipase (ref). The effects of insulin are antagonized by hormones such as adrenaline (via α2 adrenergic receptors), glucocorticoids, insulin itself, and growth hormone (somatostatin) by decreasing the affinity of insulin receptors. However, the stimulation of β2-adrenergic receptors, vagus nerve activity, and the action of incretins enhance insulin release (Verberne & Mussa, 2022).

The decision to introduce insulin in T2DM therapy will depend on some clinical signs observed in the patient. In general, insulin treatment is indicated when catabolism (e.g., ketosis and hypertriglyceridemia), decompensated hyperglycemia (polyuria, polydipsia, nocturia, and weight loss), and very high blood glucose levels (e.g., ≥ 300 m/dL or HbA1c ≥ 9%) are observed (Inzucchi, et al., 2015; Zhang, et al., 2021). In addition, insulin therapy also indicated when there is therapeutic
failure of non-insulin antidiabetics. This is when the patient no longer responds to oral drugs. The medical prescription of insulin to treat T2DM starts with the basal insulin regimen, as patients usually still produce pancreatic insulin even at very low concentrations (Fralick, et al., 2022). Thus, the Bedtime regimen (with NPH insulin) is prescribed, which means administering basal insulin at bedtime. The purpose of this treatment is to provide basal concentrations of the hormone to regulate glycemic levels during sleep and prevent the dawn phenomenon (a condition in which hyperglycemia occurs during sleep, especially in the late morning and early morning) (Peng, et al., 2022).

4. Final Considerations

The management of diabetes is individualized and should consider patient characteristics, disease severity, tissue responsiveness, and available insulin preparations (Fralick, et al., 2022). The treatment is quite complex in its prescription and execution and requires the intensive participation of the patient, the family, and the physician. In addition, non-pharmacological treatment, such as changes in lifestyle, are essential as an adjunct to pharmacological therapy. Therefore, this review didactically demonstrates the main mechanisms glycemic level regulation, the main classes of drugs currently prescribed for the treatment of T2DM, and on which pharmacological targets they act. Thus, we need novel therapies for the treatment of T2DM. Therefore, further research is needed to identify promising molecules and new drugs that are not only potent but have fewer side effects.

References


