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A minireview of pharmacotherapy of type 2 diabetes – drugs and mechanisms

Uma mini revisão da farmacoterapia do diabetes tipo 2 – fármacos e mecanismos

Una mini revisión de la farmacoterapia de la diabetes tipo 2: fármacos y mecanismos

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Abstract
Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder that originates from numerous pathogenic mechanisms, all of which result in hyperglycemia. This disease is a major cause of morbidity and mortality worldwide. Effective prevention and treatment strategies for T2DM are therefore necessary. The purpose of this review was to summarize the pharmacotherapy for patients with T2DM by discussing its pathophysiology, the therapeutic classes used in treatment strategies, as well as the mechanisms of action for each one. A literature review was conducted by searching Google Scholar, PubMed, and Science Direct databases using the search terms: type 2 diabetes mellitus, insulin, AMPK, antidiabetic drugs, incretin, SGLT2, and biguanides covering studies up to 2022. The review identified and included studies including qualitative, original research articles, and randomized controlled trial designs. The results of this study are divided into drugs that increase insulin sensitivity (e.g., biguanides, and thiazolidinediones), secretagogues (e.g., sulfonylureas, and meglitinides or glinides), incretin 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.

Resumo
O diabetes mellitus (DM2) é uma desordem metabólica crônica que se origina de inúmeros mecanismos patogênicos, resultando, todos eles, em hiperglicemia. 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 ScienceDirect 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 tiazolidinedionas), secretagogos (por exemplo, sulfonilureias e meglitinidas ou glinidas), drogas incretino miméticas (por exemplo, agonistas do receptor GLP-1 e inibidores de DPP-4), medicamentos que causam glicosúria (por exemplo, inibidores de SGLT2), medicamentos que impedem a absorção de glicose (por exemplo, inibidor de α-glicosidase) e insulina. Isso permite que os leitores entendam cada processo, mantendo o artigo concise.
Palavras-chave: Diabetes Mellitus; Controle glicêmico; Hipoglicemiantes.

Resumen
La diabetes mellitus (DM2) es un trastorno metabólico crónico que se origina por numerosos mecanismos patogénicos, todos los cuales resultan en hiperglucemia. Esta enfermedad es una de las principales causas de morbilidad y mortalidad a nivel mundial. Por lo tanto, son necesarias estrategias efectivas de prevención y tratamiento

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.

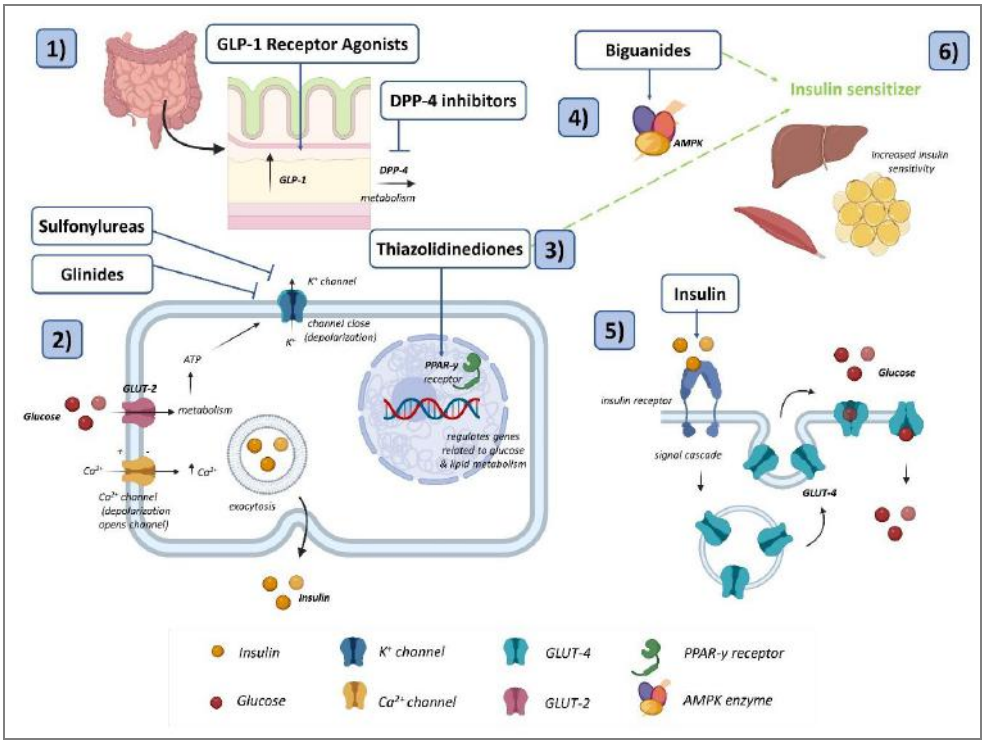
1. Introduction

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 transporter4; 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.

Database	Number of articles found up to 2022	Number of articles added to the review
Google Scholar	89	17
PubMed	54	8
Science Direct	19	3
Total	162	28

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, Vildaglipitin, 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 glycogen synthesis (Sylow, et al., 2021). In adipose tissue, insulin increases 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 hypertriglycemia), decompensated hyperglycemia (polyuria, polydipsia, nocturia, and weight loss), and very high blood glucose levels (e.g., ≥ 300m/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 potente but have fewer side effects.

References

Alexander, J. T, Staab, E. M, Wan, W. et al (2022). Longer-term Benefits and Risks of Sodium-Glucose Cotransporter-2 Inhibitors in Type 2 Diabetes: a Systematic Review and Meta-analysis. *Journal of General Internal Medicine*, 37, 439–448. Doi: 10.1007/s11606-021-07227-0.

Aslam, M., & Ladilov, L. (2022). Emerging Role of cAMP/AMPK Signaling. *Cells*, 11(2), 308. Doi: 10.3390/cells11020308.

Chandra, A., Kaur, P, Sahu, S. K., & Mittal, A. (2022). A new insight into the treatment of diabetes by means of pan PPAR agonists. Chem Biol Drug Des, 1–21. Doi: https://doi.org/10.1111/cbdd.14020.

Dawwas, G. K., Flory, J. H., Hennessy, S, Leonard, C. E., & Lewis, J. D. (2022). Comparative Safety of Sodium–Glucose Cotransporter 2 Inhibitors Versus Dipeptidyl Peptidase 4 Inhibitors and Sulfonylureas on the Risk of Diabetic Ketoacidosis. *Diabetes Care*, 45, (4), 919–927. Doi: https://doi.org/10.2337/dc21-2177.

Deng, K., & Thorn, P. (2022). Presynaptic-like mechanisms and the control of insulin secretion in pancreatic β-cells. *Cell Calcium*,104,102585. Doi: 10.1016/j.ceca.2022.102585.

Fralick, M, Jenkins, A. J, Khunti, K., et al. (2022). Global accessibility of therapeutics for diabetes mellitus. *Nature Reviews Endocrinology*, 18, 199–204. DOI: 10.1038/s41574-021-00621-y

González-González, J. G., et al. (2022). Effect of metformin on microvascular outcomes in patients with type 2 diabetes: A systematic review and meta-analysis. *Diabetes Research and Clinical Practice*, 186, 109821. Doi.org/10.1016/j.diabres.2022.109821

Hanefeld, M, Cagatay, M, Petrowitsch, T, Neuser, D, Petzinna, D, & Rupp, M. (2004). Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J*, 25, (1), 10–6. Doi:10.1016/S0195-668X(03)00468-8

Haq, F. U, Siraj, A, Ameer, M. A, et al. (2021). Comparative Review of Drugs Used in Diabetes Mellitus—New and Old. *Journal of Diabetes Mellitus*, 11, (4). Doi: 10.4236/jdm.2021.114009

Hasanvand, A. (2022). The role of AMPK-dependent pathways in cellular and molecular mechanisms of metformin: a new perspective for treatment and prevention of diseases. *Inflammopharmacology*, 30, 775–788. DOI: 10.1007/s10787-022-00980-6

Inzucchi, S. E, Bergenstal, R. M, Buse, J. B, et al. (2015). Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*, 38, (1), 140–9. Doi.org/10.2337/dc14-2441

Irudayaraj, S. S, Jincy, J, Sunil, C, et al. (2022). Antidiabetic with antilipidemic and antioxidant effects of flindersine by enhanced glucose uptake through GLUT4 translocation and PPARγ agonism in type 2 diabetic rats. *Journal of Ethnopharmacology*, 285, 114883. Doi.org/10.1016/j.jep.2021.114883

Klip, A, McGraw, T. E., & James, D. E. (2019). Thirty sweet years of GLUT4. *J. Biol. Chem*, 294, 11369-11381. Doi: 10.1074/jbc.REV119.008351

Knudsen, J. R, Steenberg, D. E, Hingst, J. R et al. (2020). Prior exercise in humans redistributes intramuscular GLUT4 and enhances insulin-stimulated sarcolemmal and endosomal GLUT4 translocation. *Mol. Metab*, 39,100998. Doi: 10.1016/j.molmet.2020.100998

Ku, E. J, Lee, D. H, Jeon, H. J & Oh, TK. (2021). Long-term effectiveness and safety of quadruple combination therapy with empagliflozin versus dapagliflozin in patients with type 2 diabetes: 3-year prospective observational study. *Diabetes Research and Clinical Practice*, 182, 109123. Doi: 10.1016/j.diabres.2021.109123

Lavania, P. (2019). A comparative study of glimepiride plus metformin versus glibenclamide plus metformin in diabetes mellitus patients. *Journal of Advanced Medical and Dental Sciences Research*, 7, (2), 157-160. Doi: 10.21276/jamdsr

Lin, EE, Scott-Solomon, E & Kuruvilla, R. (2021). Peripheral Innervation in the Regulation of Glucose Homeostasis. *Trends in Neurosciences*, 44, (3), 189-202. Doi: 10.1016/j.tins.2020.10.015

Lingvay, I, Bauer, R, Baker-Knight, J, Lawson, J & Pratley, R. (2022). An Indirect Treatment Comparison of Semaglutide 2.0 mg vs Dulaglutide 3.0 mg and 4.5 mg Using Multilevel Network Meta-regression. *The Journal of Clinical Endocrinology & Metabolism*, 107, (5), 1461–1469. Doi: 10.1210/clinem/dgab905

Min, SH, Yoon, JH, Hahn, S & Cho, YM. (2018). Efficacy and safety of combination therapy with an α-glucosidase inhibitor and a dipeptidyl peptidase-4 inhibitor in patients with type 2 diabetes mellitus: A systematic review with meta-analysis. *J Diabetes Investig*, 9, (4), 893-902. Doi: 10.1111/jdi.12754

Mone, P, Varzideh, F, Jankauskas, SS, et al. (2022). SGLT2 inhibition via empagliflozin improves endothelial function and reduces mitochondrial oxidative stress: insights from frail hypertensive and diabetic patients. *Hypertension*,79, (8), 1633–1643. Doi: 10.1161/HYPERTENSIONAHA.122.19586

Peng, F, Li, X, Xiao, F, Zhao, R & Sun, Z. (2022). Circadian clock, diurnal glucose metabolic rhythm, and dawn phenomenon. *Trends in Neurosciences*, 45, (6), 471-482. Doi.org/10.1016/j.tins.2022.03.010

Pullen, RA, Lindsay, DG, Wood, SP, Tickle, IJ et al. (1976). Receptor-binding region of insulin. *Nature*, 259, 369-373.

Saltiel, AR. (2021). Insulin signaling in health and disease. *J Clin Invest*,131, (1), e142241. Doi: 10.1172/JCI142241

Scheen, AJ. (2021). Sulphonylureas in the management of type 2 diabetes: To be or not to be? *Diabetes Epidemiology and Management*, 1, 100002. Doi.org/10.1016/j.deman.2021.100002

Shyng, SL. (2022). KATP Channel Function: More than Meets the Eye. *Function*, 3, (1), zqab070. Doi.org/10.1093/function/zqab070

Svitlana, D, Kateryna, K, Iryna, B, et al. (2021). Potential risks and pharmacological safety features of hypoglycemic drugs. *Archives*, 2, 1164-1171.

Sylow, L, Tokarz, VL, Richter, EA & Klip, A. (2021). The many actions of insulin in skeletal muscle, the paramount tissue determining glycemia. *Cell Metabolism*, 33, (4), 758-780. Doi: 10.1016/j.cmet.2021.03.020

Tomlinson, B, Patil, NG, Fok, M, Chan, P & Lam, CWK. (2022). The role of sulfonylureas in the treatment of type 2 diabetes. *Expert Opinion on Pharmacotherapy*,23, (3), 387-403. Doi.org/10.1080/14656566.2021.1999413

Verberne, AJM & Mussa, BM. (2022). Neural control of pancreatic peptide hormone secretion. *Peptides*, 152, 70768. Doi.org/10.1016/j.peptides.2022.170768

Wei, Y, Lin, F, Lin, S & Wang, C. (2018). Concomitant use of Repaglinide and Clopidogrel and risk of hypoglycemia: a population-based nested case-control study. *Value in Health*, 21, S1–S115. Doi.org/10.1016/j.jval.2018.07.276

Wharton, S, Davies, M, Dicker, D, et al. (2021). Managing the gastrointestinal side effects of GLP-1 receptor agonists in obesity: recommendations for clinical practice. *Postgraduate Medicine*, 134, (1), 14-19. Doi: 10.1080/00325481.2021.2002616

Yau H, Rivera K, Lomonaco R & Cusi K. (2013). The future of thiazolidinedione therapy in the management of type 2 diabetes mellitus. *Curr Diab Rep*,13, (3), 329-41.

Zhang, Y, Fu, T, Mu, YM, et al. (2021). Network Meta-analysis of the Therapeutic Effects of Hypoglycemic Drugs and Intensive Lifestyle Modification on Impaired Glucose Tolerance. *Clinical Therapeutics*, 43, (9), 1524-1556. Doi: 10.1016/j.clinthera.2021.07.014