International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

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ARTICLE TITLE	THE COMPREHENSIVE COMPARISON OF THE EFFICACY OF FIRST-LINE DRUGS IN THE TREATMENT OF TYPE II DIABETES: METFORMIN, GLP-1 AGONISTS, AND SGLT2 INHIBITORS
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3884
RECEIVED	17 August 2025
ACCEPTED	27 September 2025
PUBLISHED	30 September 2025
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THE COMPREHENSIVE COMPARISON OF THE EFFICACY OF FIRST-LINE DRUGS IN THE TREATMENT OF TYPE II DIABETES: METFORMIN, GLP-1 AGONISTS, AND SGLT2 INHIBITORS

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ABSTRACT

Introduction: Type II diabetes is a chronic metabolic disease characterized by hyperglycemia. The goal of diabetes treatment is to achieve normal blood glucose levels and prevent complications arising from diabetes. Currently, there are many groups of antidiabetic drugs available, differing in their main indications for use, mechanism of action, and side effects, which allow the selection of the most effective and best tolerated treatment method for a specific patient.
Objective: The objective of this review was to compare the efficacy of drugs used as first-line treatments for type II diabetes, namely metformin, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors, also known as flozins, taking into account their limitations and adverse effects.
Method: In order to compare the effectiveness of metformin, GLP-1 agonists, and SGLT2 inhibitors in the treatment of type II diabetes, a systematic review was conducted between 2020 and 2025, covering the PubMed database. Key words such as type II diabetes, metformin, GLP-1 receptor agonist, MALA, SGLT2 inhibitors were used.
Conclusions: The comparison shows that metformin, GLP-1 agonists, and SGLT2 inhibitors are effective drugs used in the treatment of type II diabetes, and the choice of the appropriate drug depends on the patient's condition, comorbidities, and the desired effects. SGLT2 inhibitors are the best choice for patients with heart failure and renal failure, while GLP-1 agonists are the most suitable for patients with high cardiovascular risk, as they reduce the risk of heart attack or stroke. Metformin, by increasing the sensitivity of peripheral tissues to insulin, is used in the treatment of both diabetes and insulin resistance. In addition, it is the cheapest of the compared groups of drugs, which may be an important aspect in the selection of therapy for individual patients coming from poor environments. All three groups lower blood glucose without the risk of hypoglycemia. Side effects mainly include gastrointestinal disorders (metformin, GLP-1) and urinary tract infections (SGLT2). Summing up the above conclusions, it can be stated that the choice of drug in diabetes therapy should mainly depend on the patient's comorbidities.

KEYWORDS

Type II Diabetes, Metformin, GLP-1 Receptor Agonist, MALA, SGLT2 Inhibitors

CITATION

Anna Kamieniak, Dominika Gieroba. (2025). The Comprehensive Comparison of the Efficacy of First-Line Drugs in the Treatment of Type II Diabetes: Metformin, GLP-1 Agonists, and SGLT2 Inhibitors. *International Journal of Innovative Technologies in Social Science*, 3(47). doi: 10.31435/ijitss.3(47).2025.3884

Introduction

Epidemiology

Diabetes is the most widespread civilisation disease in the world. By 2000, there were 171 million cases of diabetes worldwide, in 2011 the number was 346 million, and in 2014 - 422 million. Scientists predict that by 2030, the number of diabetes cases will exceed 500 million [1], and by 2045, 700 million [2].

Pathophysiology

Diabetes is a diverse group of chronic metabolic diseases characterized by hyperglycemia resulting from impaired insulin secretion or action. [2] According to the 1999 classification, modified in 2019, the WHO distinguishes between the following types of diabetes: type I diabetes, type II diabetes, hybrid forms of diabetes, and other specific types of diabetes. Type I diabetes develops as a result of the destruction of the pancreatic islet β cells by immune system cells. The pancreatic islet β cells are responsible for insulin production and their destruction leads to complete insulin deficiency. In type II diabetes, hyperglycemia occurs as a result of insulin resistance combined with relative insulin deficiency or abnormal insulin secretion, which may be accompanied by insulin resistance. [3] Insulin resistance is a condition in which the body's cells are less sensitive to insulin, despite normal or even elevated blood insulin levels. Insulin-stimulated glucose uptake by peripheral tissues is reduced, resulting in persistently high blood glucose levels. [2] Type II diabetes often remains undiagnosed for many years because hyperglycemia develops gradually, initially showing no symptoms. The risk of developing the disease increases with age, in people who are overweight, have poor eating habits, and are physically inactive. [4]

Diagnostic criteria

The normal fasting blood glucose level is 70-99 mg/dl. Values outside this range are abnormal. Diabetes is diagnosed when:

1. fasting blood glucose measured twice on different days is ≥ 126 mg/dl (7.0 mmol/l),
2. glycemia after a 2-hour OGTT test ≥ 200 mg/dl (≥11.1 mmol/l),
3. random glycemia ≥ 200 mg/dl (≥11.1 mmol/l) and accompanying symptoms of hyperglycemia,
4. HBA1c value ≥ 6.5% (48 mmol/mol). [4]

Complications

Long-term diabetes carries numerous complications in the form of micro- and macroangiopathy. Microangiopathy includes: nephropathy, retinopathy, and neuropathy. Diabetic nephropathy causes both functional and morphological changes in kidney tissue. As a result of glomerular sclerosis and interstitial tubular fibrosis, a gradual deterioration of kidney function occurs. It is manifested by albuminuria and a decrease in eGFR. Diabetic retinopathy occurs in 20% of patients at the time of diagnosis of diabetes. It is caused by hyperglycemia-induced damage to the connections between endothelial cells and apoptosis and detachment of pericytes. Diabetic neuropathy manifests itself with pain, burning, tingling, and numbness in the limbs. It can lead to hyperalgesia and mechanical allodynia, as a result of which even minor stimuli can cause pain. Other complications include non-alcoholic fatty liver disease, liver fibrosis, cognitive impairment, and pulmonary fibrosis, which can be a late complication of diabetes. [4]

Metformin

Metformin (1,1-dimethylbiguanide hydrochloride) is the most common drug used to treat type II diabetes, described by the WHO as an “essential medicine.” The first mentions of metformin synthesis date back to 1922, and in 1957, French physician Jean Sterne pioneered the use of metformin in the treatment of type II diabetes. [5] [6]

It is administered orally 1-3 times a day in doses ranging from 500 mg to 3 g per day. In patients taking doses of 1 g/day to 2 g/day, the plasma concentration of metformin ranges from 10 μM to ~40 μM, with studies showing that therapeutic plasma concentrations of metformin ranged from ~1 μM to ~700 μM. Its bioavailability is approximately 50-60% and its plasma half-life is 6 hours. It is mainly eliminated by the kidneys, with approximately 90% of metformin being eliminated within 24 hours. It accumulates in the small intestine, liver, and kidneys. [5] [7]

The main mechanism of metformin is to inhibit hepatic gluconeogenesis and increase insulin-stimulated glucose uptake by skeletal muscles. In order for metformin to cross the plasma membrane, special

transmembrane transporters are required. Studies have shown that transporters such as OCT1, OCT3, and MATE1, which are found in the liver, kidneys, and intestines. Metformin regulates hepatic gluconeogenesis through four mechanisms: transcriptional, allosteric, substrate, and redox.

Due to its favorable safety profile, it lowers blood glucose levels without causing hypoglycemia in patients. [5] In addition, it has a beneficial effect on the cardiovascular system and slightly reduces weight gain. [6]

According to a randomized double-blind study, metformin affects the gut microbiota, both in terms of its composition and function. The study showed that short-term use of metformin resulted in a reduction in the amount of Bacteroides fragilis bacteria, which in turn caused an increase in glycosidic acid (GUDCA). Higher concentrations of glycosidic acid inhibit the farnesoid X receptor (FXR) – inhibition of this receptor increases tissue sensitivity to insulin and facilitates glucose uptake from the blood. [8]

Metformin also has a beneficial effect on the cardiovascular system. It has a positive effect on the condition of the heart muscle by improving lipid and glucose metabolism via AMPK. It reduces HDL dysfunction, which contributes to the improvement of cholesterol transport, reduces oxidative stress, and alleviates inflammation caused by hyperglycemia. [8]

Metformin is a relatively safe drug, yet it should not be used in certain clinical situations. These include: shock, acute myocardial infarction, uncompensated heart failure, acute respiratory failure, severe liver failure, and alcohol poisoning. In the above-mentioned conditions, tissue oxygen demand increases, which is associated with elevated lactate production, and improper use of metformin may contribute to increased lactate production and the risk of developing lactic acidosis. [7] In addition, metformin is contraindicated in renal failure. In patients with eGFR < 30 ml/min/1.73 m2, there may be reduced excretion of metformin and its increased accumulation - elevated plasma metformin concentrations exceeding 4 mg/l increase the risk of developing lactic acidosis. [9]

Metformin-associated lactic acidosis (MALA) is an acute condition which, if not treated properly, can even lead to death. It is characterized by a decrease in blood pH < 7.35 with arterial blood lactate concentration > 5 mmol/l and blood metformin concentration > 5 mg/l. [7] Treatment consists of immediate discontinuation of metformin, supportive care (oxygen therapy, intravenous bicarbonate infusion, fluid therapy, blood transfusion), treatment of concomitant causes of acidosis, and in severe cases of MALA, extracorporeal elimination of metformin by hemodialysis. [9]

The use of metformin during pregnancy still gives rise to controversy. Metformin crosses the placenta, so it should not be the first-choice drug, yet its use during pregnancy is becoming increasingly common worldwide. According to studies conducted to date, children of mothers treated with metformin during pregnancy may be more likely to develop obesity, including abdominal obesity, and hypertension. [8]

Glucagon-like peptide-1 (GLP-1) receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists are new drugs commonly used to treat type II diabetes. They are divided into two basic groups: polypeptide and non-polypeptide agonists. Polypeptide agonists are divided into GLP-1 and derivatives, and exendin-4 and derivatives, based on similarities in their amino acid sequence. [10]

The mechanism of action of all drugs in this group is based on increasing hyperglycemia-induced insulin secretion, inhibiting glucagon secretion in euglycemia and hyperglycemia, slowing gastric emptying, which prevents rapid increases in blood glucose after a meal, and contributing to lower calorie intake, thus reducing body weight. [11]

GLP-1 agonists used in clinical practice include:

- short-acting: Lixisenatide, oral Semaglutide, Exenatide
- long-acting: Exenatide, Liraglutide, Semaglutide, Abiglutide, Taspoglutide, Dulaglutide

Short-acting agonists delay gastric emptying, thereby lowering postprandial glucose concentrations, while long-acting agonists increase insulin production and reduce glucagon production. It contributes to lower glucose concentrations after meals and when fasting. [12]

Liraglutide is recommended by the American Diabetes Association guidelines as a second-line drug (after metformin) in patients with diabetes and concomitant cardiovascular atherosclerotic disease. [10] According to studies conducted in patients with type 2 diabetes who were at high risk of cardiovascular events, cardiovascular deaths occurred in fewer patients in the liraglutide group (4.7%) compared to the placebo group (6%), and the all-cause mortality rate was also lower in the liraglutide group (8.2%) than in the placebo group (9.6%). [13]

A randomized study conducted in 2015 showed a positive effect of taspoglutide on lowering total cholesterol, LDL cholesterol, and triglycerides. Liraglutide at a dose of 1.2 mg/d also showed a positive effect on lipid metabolism and reduced cardiovascular risk.

GLP-1 analogues delay the development of chronic kidney disease and diabetic nephropathy: they slow down the decline in glomerular filtration rate and delay the onset of proteinuria. According to studies, semaglutide had a particularly beneficial effect on kidney function, with a 46% reduction in macroalbuminuria, while liraglutide caused a 22% reduction in macroalbuminuria.

The use of semaglutide, commonly known under the trade name Ozempic, showed significant weight loss compared to liraglutide and exenatide. The feeling of greater satiety is caused by delayed gastric emptying, as well as the activation of gastric receptors, which use the vagus nerve to inhibit the satiety center receptors located in the brain stem. Its effectiveness in reducing body weight and its favorable safety profile have made semaglutide the first GLP-1 agonist used chronically for weight loss. [14]

The use of GLP-1 agonists during pregnancy is not recommended. Studies in rats, mice, and rabbits have shown reduced fetal growth and body weight, as well as delayed and impaired ossification of the fetal skeleton. All GLP-1 analogues used in animals during late pregnancy and lactation caused reduced fetal growth and weight loss. However, no systematic reviews on the use of GLP-1 agonists during pregnancy and lactation have been conducted to date. Data on the use of GLP-1 analogues during pregnancy are limited, involving a small number of pregnancies, and there are no detailed data on exposure. Given the availability of other drugs with a proven safety profile, the use of GLP-1 analogues by pregnant and breastfeeding women is not recommended. [15]

SGLT2 inhibitors (flozins)

SGLT2 inhibitors (also known as flozins) are a new group of drugs that were originally indicated for the treatment of type 2 diabetes, but in recent years, they have also shown positive and promising effects in the treatment of heart failure and chronic kidney disease. [16] They work by inhibiting sodium-glucose cotransporters (SGLT) in the proximal tubule (PCT) of the kidney and in the intestinal epithelium. Among them, sodium-glucose cotransporter 2 (SGLT2) is mainly expressed in segments S1 and S2 of the proximal tubule, where it plays a key role in renal glucose reabsorption. [17] SGLTs are sodium-glucose transporters present in the luminal membrane of the proximal tubule, which are responsible for the reabsorption of approximately 180 g of glucose per day. SGLT2 inhibitors reduce this process by 50-60%, leading to glucose excretion in the urine and lowering blood glucose and HbA1c in patients with T2DM. [18] The flozin group includes dapagliflozin, empagliflozin, and canagliflozin, among others. [17]

Numerous studies involving SGLT2 inhibitors have provided evidence of their beneficial effects on the kidneys and cardiovascular system, regardless of baseline renal function, cardiovascular risk, or glycemic control. For example, the CREDENCE study confirmed that treatment with canagliflozin in patients with type 2 diabetes, albuminuria, and impaired renal function significantly reduces the risk of ESKD, increases in creatinine concentration, and renal deaths by approximately 30% and significantly slows the decline in eGFR (by more than 2.5 ml/min/year) compared to placebo. Similar effects were observed in the DAPA-CKD study, which included patients with chronic kidney disease with and without type 2 diabetes. The study was terminated prematurely due to clear benefits – dapagliflozin reduced the risk of renal function deterioration by 39% – demonstrating for the first time that patients without diagnosed type 2 diabetes can also benefit from treatment with flozins. [19]

SGLT2 inhibitors significantly reduce the risk of cardiovascular death or first hospitalization for heart failure. It is approximately 20–23% reduction, as it was demonstrated in a meta-analysis of five large outcomes studies (DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, SOLOIST-WHF) and in a combined analysis of two major studies: DAPA-HF and EMPEROR-Reduced, involving as many as 12,251 patients. This effect applies to both a decrease in hospitalizations due to heart failure and a reduction in cardiovascular deaths, and the benefits are observed regardless of ejection fraction, age, gender, or kidney function. In addition, patients treated with flozins experience an improvement in quality of life more often, and the incidence of serious adverse events is low and comparable to placebo. The greatest benefits are seen in NYHA class II patients, although the positive effect also persists in classes III/IV. [20]

Although flozins have proven benefits in protecting the kidneys and heart, their use is also associated with the risk of the occurrence of adverse effects. The most important of these are: an increased risk of genitourinary infections, including fungal infections, and diabetic ketoacidosis. [21]

The adverse effects of SGLT2 inhibitors are mainly caused by the glucosuria. The presence of glucose in the urine creates a favorable environment for the growth of bacteria and fungi, which increases the risk of urinary tract infections and fungal infections of the genital organs. Studies have shown that the addition of glucose to urine increases the growth of uropathogenic E. coli bacteria and stimulates the proliferation of fungi such as Candida albicans. [22]. In addition, the excretion of glucose in the urine lowers its concentration in the blood and at the same time reduces the need for insulin. Lower insulin concentrations and a relative increase in glucagon promote increased lipolysis and ketogenesis. As a result, ketone bodies may accumulate and diabetic ketoacidosis (including euglycemic ketoacidosis) may develop. This requires rapid diagnosis and treatment, including discontinuation of SGLT2 inhibitor therapy, administration of insulin, and rehydration of the patient. [23]

Some studies (e.g., CANVAS) have also pointed to an increased risk of lower limb amputation and fractures, although this has not been clearly confirmed in other analyses. Cases of dehydration, hypotension, and increased creatinine levels at the beginning of therapy have been reported less frequently. [21]

Studies have also shown that SGLT2 inhibitors (EMPA, DAPA, CANA) cross the placenta and enter the fetal circulation, with DAPA crossing the fastest. These drugs do not significantly affect glucose metabolism or β-hCG production, but they do reduce leptin secretion, which may be important for placental function. The use of SGLT2 inhibitors may lead to renal pelvis and tubule dilation, congenital malformations, and an increased risk of miscarriage. These findings support the recommendation not to use these drugs during pregnancy and breastfeeding. Especially when one takes into account that there are effective and safe alternatives. Last but not least, further research on the use of these drugs during pregnancy is required. [25]

	Metformin	GLP-1 agonist	SGLT2 inhibitor
Main mechanism of action	inhibition of hepatic gluconeogenesis, increased peripheral tissue sensitivity to insulin	increased insulin secretion induced by hyperglycemia	reduction of glucose reabsorption in the proximal tubule of the nephron - induction of glucosuria without accompanying hyperglycemia
Effect on plasma insulin	↓	↑	↓
Risk of hypoglycemia	none	none	none
Body weight	↓ / no change	↓	↓
Cardiovascular system	beneficial effect	Liraglutide - beneficial effect	Empagliflozin, canagliflozin - beneficial effect
Renal failure	contraindicated in eGFR ≤ 30 ml/min/1.73 m2	beneficial effect on the kidneys	beneficial effect on the kidneys
Safety during pregnancy	crosses the placenta to the fetus, should not be used as a first-line drug	reduces fetal survival, body weight, growth, and skeletal ossification, and may cause serious birth defects	increased risk of miscarriage and birth defects,enlargement of the renal pelvis and tubules
Cost of treatment	low	medium-high	medium

Other drug groups

If the above-mentioned drug groups do not produce satisfactory results in the treatment of type 2 diabetes, therapy should be intensified. A new group of drugs includes DPP4 inhibitors (gliptins). These are oral drugs that work by blocking the DPP-4 enzyme responsible for the inactivation of incretin hormones, mainly GLP-1 and GIP. This prolongs their action, leading to increased glucose-dependent insulin secretion and reduced glucagon secretion, resulting in improved glycemic control. In addition, they also have beneficial effects on

the cardiovascular system, including improving endothelial function, reducing oxidative stress, and exhibiting anti-inflammatory effects, which may be important in the treatment of heart failure. Gliptins are generally well tolerated and do not cause weight gain. The most commonly observed side effects include mild gastrointestinal disorders, rash, and upper respiratory tract infections. However, the effect of lowering HbA1c is moderate and lesser than in the case of GLP-1 agonists. [26]

It should be noted that SGLT2 inhibitors, GLP-1 agonists, and DPP4 inhibitors reduce overall mortality and the risk of serious cardiovascular events in adults with type 2 diabetes. SGLT2 inhibitors additionally reduce the progression of kidney disease, number of hospitalizations due to heart failure, and severe hypoglycemia, while GLP-1 agonists reduce the risk of stroke. DPP4 inhibitors do not show such benefits. [27]

Another drug is tirzepatide, which acts simultaneously on GLP-1 and GIP receptors, improving glycemic control in people with type 2 diabetes. Numerous clinical trials have shown that at a dose of 15 mg, it reduces HbA1c by up to 2.58%, and more than half of patients achieve normoglycemia with minimal risk of severe hypoglycemia. The drug also has a strong weight loss effect – in the SURMOUNT-1 study in overweight or obese individuals without diabetes, 85–91% of participants lost at least 5% of their body weight, and the highest dose of 15 mg resulted in an average weight loss of 20.9%. Tirzepatide also improves blood pressure, lipid profile, BMI, and waist circumference. The most common side effects are related to the gastrointestinal tract. These include nausea, vomiting, diarrhea, and decreased appetite. In addition, research suggests that tirzepatide may also be useful in the treatment of heart failure and fatty liver disease. [28]

It is also important to remember that non-pharmacological methods of treating type 2 diabetes include a wide range of measures to support glycemic control and improve metabolic health. Regular physical activity, especially a combination of aerobic and resistance exercises, improves insulin sensitivity, glycemic control, and muscle function. Changes in nutrition, such as reducing calorie intake, increasing protein consumption, or following diets such as the Mediterranean or low-carbohydrate diets, have a beneficial effect on glucose metabolism. In obese patients, bariatric surgery can be effective. It often leads to remission, especially in cases with a shorter disease duration and no previous insulin therapy. [26]

Summary

Metformin, GLP-1 agonists, and SGLT2 inhibitors all effectively lower blood glucose levels without causing hypoglycemia. In addition, metformin contributes to a decrease in plasma insulin concentration and improves tissue sensitivity to insulin, which is useful in the treatment of insulin resistance. All three groups of drugs have a beneficial effect on the cardiovascular system, but in the case of metformin, this effect is the smallest. SGLT2 inhibitors achieve the best effect in patients with heart failure as these significantly reduce the risk of hospitalization due to heart failure. GLP-1 agonists reduce the risk of major cardiovascular events such as heart attack, stroke, or death due to a vascular event. In addition, SGLT2 inhibitors slow down the progression of chronic kidney disease to the greatest extent, regardless of the initial eGFR value. GLP-1 analogues also have a beneficial effect on the kidneys, but their effect in this regard is weaker than that of SGLT2 inhibitors. In the case of renal impairment with an eGFR value, it is not recommended to include metformin in the treatment. Furthermore, these drugs have a positive effect on weight reduction, with GLP-1 analogues showing the best results. Despite numerous positive health effects, all three groups of drugs have side effects, such as gastrointestinal disorders when starting treatment with metformin and GLP-1 analogues, or frequent urinary tract infections in the case of SGLT2 inhibitors. Each of the three groups mentioned has a negative impact on fetal development, so these drugs should not be used during pregnancy. The choice of the appropriate group of drugs should be tailored to the patient's clinical and medical conditions, and the treatment effects we aim to achieve. We should individually select the drug appropriate for a given person, taking into account the patient's chronic diseases, cardiovascular conditions and the degree of renal impairment.

Abbreviations:
OCT1 - Organic Cation Transporter 1
OCT3 - Organic Cation Transporter 3
MATE1 - Multidrug and Toxin Extrusion Protein 1
GUDCA - Glycosidic Acid
FXR - Farnesoid X receptor
MALA - Metformin-Associated Lactic Acidosis
SGLT2 - Sodium-Glucose Linked Transporter 2

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Supervision: Anna Kamieniak
Project administration: Dominika Gieroba
Funding Acquisition: Not applicable

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This Research received no external funding.
Institutional Review Board Statement: Not applicable
Informed Consent Statement: Not applicable.
Data Availability Statement: Not applicable.
Conflicts of Interests: The authors declare no conflict of interest.

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