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Optimizing Glycemic Control in Type 2 Diabetes: A Review of Metformin-Based Combination Regimens

Kahled Ali Ajala [1]* ، Mohammed Alsunci Alshriaf [2]
[1] Department of Medical Laboratories Technology, Faculty of Health Sciences, Al-khoums, ElMergib University, Libya
[2] Department of Medical Laboratories, Faculty of Medical Technology, Al-khoums, ElMergib University, Libya
kaajalah@elmergib.edu.ly

تحسين التحكم في نسبة السكر في الدم لدى مرضى السكري من النوع الثاني: مراجعة للأنظمة العلاجية المركبة القائمة على الميتفورمين

خالد علي عجالة [1] * ، محمد السنوسي الشريف [2]
[1] قسم تقنية المعامل الطبية ، كلية العلوم الصحية ، جامعة المرقب ، الخمس ، ليبيا
[2] قسم المختبرات الطبية ، كلية التقنية الطبية ، جامعة المرقب ، الخمس ، ليبيا

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Abstract:
Background: Type 2 Diabetes Mellitus (T2DM) is a prevalent chronic metabolic disorder characterized by persistent hyperglycemia, contributing to significant morbidity and mortality worldwide. While metformin remains the first-line pharmacologic treatment, the complex nature of T2DM often necessitates combination therapy to optimize glycemic control and minimize adverse effects. Objective: This review aims to evaluate the combined effects of metformin with various classes of antidiuretic agents on key clinical parameters, including glycemic control, weight changes, and hypoglycemia incidence in patients with T2DM. Methods: A comprehensive review of recent clinical trials and meta-analyses was conducted, focusing on the efficacy and safety profiles of metformin when combined with DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 receptor agonists, sulfonylureas, and insulin. Comparative analysis was performed regarding glycemic outcomes, impact on body weight, and hypoglycemia risk. Results: Findings indicate that metformin combined with DPP-4 inhibitors, SGLT-2 inhibitors, or GLP-1 receptor agonists significantly improves and sustains glycemic control, with added benefits of weight reduction or neutrality and a low incidence of hypoglycemia. Conversely, combinations of metformin with sulfonylureas or insulin also enhance glycemic management but are associated with increased risk of hypoglycemia and weight gain in some patients. Conclusions and Recommendations: Individualized treatment selection is critical in determining the optimal combination therapy to enhance clinical outcomes while minimizing adverse effects in T2DM. Further long-term studies are warranted to explore new combinations and their impacts on patient quality of life and disease progression.

Keywords: Diabetes Mellitus, Type 2 Diabetes Mellitus, Combination Therapy, Glycemic Control, Antidiuretic Drugs.

الملخص:
الخلفية: يُعد داء السكري من النوع الثاني (T2DM) اضطرابًا أيضيًا مزمنًا شائعًا يتميز بارتفاع مستمر في سكر الدم، مما يُسهم في ارتفاع كبير في معدلات الاعتلال والوفيات عالميًا. وبينما يظل الميتفورمين العلاج الدوائي الأول، فإن الطبيعة المعقدة لداء السكري من النوع الثاني غالبًا ما تتطلب علاجًا مركبًا لتحسين ضبط سكر الدم وتقليل الآثار الجانبية. **الهدف**: تهدف هذه الدراسة إلى تقييم الآثار المشتركة للميتفورمين مع فئات مختلفة من الأدوية الخافضة لسكر الدم على المعايير السريرية الرئيسية، بما في ذلك ضبط سكر الدم، وتغيرات الوزن، ومعدلات نقص سكر الدم لدى مرضى داء السكري من النوع الثاني. **المنهجية**: أُجريت مراجعة شاملة للتجارب السريرية الحديثة والتحليلات التلوية، مع التركيز على فعالية وسلامة الميتفورمين عند استخدامه مع مثبطات4-DPP ، ومثبطات2-SGLT ، ومنبهات مستقبلات1-GLP ، والسلفونيل يوريا، والأنسولين. أُجري تحليل مقارن لنتائج قياس نسبة السكر في الدم، وتأثيرها على وزن الجسم، وخطر نقص سكر الدم. **النتائج**: تشير النتائج إلى أن الميتفورمين، بالإضافة إلى مثبطات4-DPP ، أو مثبطات2-SGLT ، أو منبهات مستقبلات1-GLP ، يُحسّن بشكل ملحوظ ويُحافظ على ضبط نسبة السكر في الدم، مع فوائد إضافية تتمثل في إنقاص الوزن أو موازنة مستوى السكر في الدم، وانخفاض معدل حدوث نقص سكر الدم. في المقابل، تُحسّن توليفات الميتفورمين مع السلفونيل يوريا أو الأنسولين أيضًا من إدارة نسبة السكر في الدم، ولكنها ترتبط بزيادة خطر نقص سكر الدم وزيادة الوزن لدى بعض المرضى. **الخلاصة والتوصيات**: يُعد اختيار العلاج المُخصص لكل مريض أمرًا بالغ الأهمية في تحديد العلاج المُركب الأمثل لتحسين النتائج السريرية مع تقليل الآثار الجانبية في مرض السكري من النوع الثاني. هناك حاجة إلى مزيد من الدراسات طويلة الأمد لاستكشاف توليفات جديدة وتأثيراتها على جودة حياة المريض وتطور المرض.

الكلمات الدالة: داء السكري، داء السكري من النوع 2، العلاج المركب، التحكم في نسبة السكر في الدم، الأدوية المضادة لمرض السكر.

Introduction

A major global health concern that affects millions of people worldwide is diabetes mellitus, a chronic metabolic disease marked by increased blood glucose levels. with improvements in treatment methods, reaching ideal glycemic control frequently calls for a multimodal strategy that combines medication, dietary changes, and lifestyle adjustments. of its effectiveness, safety record, and affordability, metformin is a mainstay treatment among the several kinds of antidiabetic drugs (Chen et al., 2015).

Nonetheless, as diabetes treatment advances, more people are interested in investigating the possible synergy of taking metformin in combination with other classes of antidiabetic medications. This strategy targets multiple pathophysiological pathways at once in an effort to treat the multifaceted character of diabetes mellitus in addition to improving glycemic control (Chowdhury & Hussain, 2019; Alam et al., 202). Investigating combined treatment with other antidiabetic medications, such as metformin, is a promising approach to improving treatment outcomes for diabetes mellitus is the investigation of combination therapy, which combines metformin with additional antidiabetic medications. Researchers and clinicians can learn a great deal about the possible advantages and difficulties of such treatment regimens by assessing the combined effects of these drugs on a variety of parameters, including lipid profiles, insulin sensitivity, glycemic control, and cardiovascular risk factors (Da Rocha et al., 2020; Dludla et al., 2020).

1.1 Importance of the Study

The value of this study rests in its ability to inform clinical decision-making processes, optimizing therapeutic methods for managing type 2 diabetes. Understanding the complex effects of antidiabetic medication combinations is essential for adjusting therapies to the needs of specific patients, increasing efficacy, and reducing side effects, as the prevalence of diabetes rises worldwide (Choi & Chung, 2016; Sinclair et al., 2020; Chandrasekaran & Weiskirchen, 2024).

1.2 Problem of the Study

Even though metformin is frequently used in conjunction with other antidiabetic medications, little is known about how these combinations differ in their effects on key health metrics. Healthcare professionals' capacity to optimize diabetes management techniques catered to each patient's specific profile is hampered by this information gap (Deng & Thorn, 2022; Jacobs et al., 2024;).

1.3 Objective of the Study

This study's main goal is to methodically examine and contrast how different classes of antidiabetic medications interact with metformin in terms of important health outcomes, such as glycemic control, body weight fluctuations, and the prevalence of hypoglycemia.

1.4 Hypothesis

H0: Null Hypothesis: Using metformin by itself or in combination with other antidiabetic medications has no discernible effect on health metrics.

H1: Alternative hypothesis: Compared to taking metformin by itself, using it in combination with other classes of antidiabetic medications has a considerable impact on health metrics.

1.5 Definition of Terms

• Metformin: A member of the biguanide class, this drug is mainly prescribed as a first-line treatment for type 2 diabetes, especially in patients who are overweight (Christensen & Gannon, 2019).

• Antidiabetic Drugs: These medications reduce blood glucose levels to treat diabetes mellitus.

• Glycemic Control: Managing blood sugar levels in diabetics, often as shown by HbA1c readings.

• Hypoglycemia: A disorder marked by an unusually low blood sugar (glucose) level.

• Synergistic Effects: When two or more agents or forces interact, their combined effect is higher than the sum of their separate effects. This is known as a synergistic effect) Galicia-Garcia et al., 2020; Ghiasi et al., 2019).

2. literature Review:

2.1 Definition of Diabetes Mellitus

Chronic hyperglycaemia is a hallmark of a set of metabolic diseases collectively referred to as diabetes mellitus. A disruption in either insulin action or secretion, or both, is usually the cause (Kanellis & Kang, 2005).

2.2 Diabetes Mellitus Classification

Diabetes mellitus, are classified into several categories based on its causes and how it presents clinically:

• Type 1 Diabetes: An autoimmune condition where the immune system attacks insulin-producing cells in the pancreas. It often develops in childhood or adolescence but can occur at any age.

• Type 2 Diabetes: The most common form, usually linked to lifestyle factors such as obesity and inactivity. It involves insulin resistance and often progresses with reduced insulin production.

• Gestational Diabetes Mellitus (GDM): Occurs during pregnancy and usually resolves after childbirth. However, it can increase the risk of developing type 2 diabetes later in life.

• Monogenic Diabetes: A rare form caused by mutations in a single gene, affecting how the body produces or uses insulin.
• Secondary Diabetes: Develops as a result of other medical conditions or treatments, such as pancreatic diseases, hormonal disorders, or certain medications. (Da Rocha et al., 2020; Dludla et al., 2020; Dludla et al., 2020).

2.2.1 Type 1 Diabetes Mellitus (T1DM)

T1DM, which makes up 5% to 10% of all cases of diabetes mellitus (DM), is characterized by autoimmune destruction to the beta cells in the pancreatic islets that produce insulin. As a result, there is absolutely no insulin. Genetic predisposition and environmental factors like viruses, poisons, or specific foods have been connected to autoimmune disease. T1DM can manifest at any age, however it is more common in children and teenagers (Galicia-Garcia et al., 2020; Ghiasi et al., 2019).

2.2.2 Type 2 of Diabetes Mellitus

About 90% of diabetes cases are caused by type 2 diabetes mellitus (T2DM). The decreased sensitivity to insulin that defines type 2 diabetes is known as insulin resistance. Insulin is ineffective in this state, and in order to maintain glucose homeostasis, insulin production initially rises. However, over time, insulin production falls, resulting in type 2 diabetes. T2DM is the most common kind (Schleicher et al., 2022; Deng & Thorn, 2022; Jacobs et al., 2024;).

2.2.3 Diabetes Mellitus During

Gestational diabetes mellitus (GDM) or hyperglycemia in pregnancy are terms used to describe hyperglycemia that is initially diagnosed during pregnancy (Sweeting et al., 2022). The second and third trimesters of pregnancy are the most likely times for gestational diabetes to occur, while it can happen at any time. The American Diabetes Association (ADA) estimates that GDM complicates 7% of pregnancies (Moon & Jang, 2022). Women with gestational diabetes and their offspring are at a higher risk of developing type 2 diabetes mellitus in the future (Blahova & associates, 2021; Zheng et al., 2018).

Hypertension, preeclampsia, and hydramnios can exacerbate GDM, and it may also lead to a rise in surgical procedures. The fetus may have congenital defects or macrosomia. Even after birth, these babies may experience respiratory distress syndrome and childhood and teenage obesity after birth. Advanced age, obesity, significant prenatal weight gain, a history of stillbirth or congenital abnormalities in previous babies, or a family history of diabetes are risk factors for GDM (Alam et al., 2021; Hussain & Chowdhury. 2019).

2.2.4 Monogenic Diabetes

One mutation inside an autosomal dominant gene causes this type of diabetes. Neonatal diabetes mellitus and young-onset maturity-onset diabetes (MODY) are two types of monogenic diabetes. Monogenic diabetes accounts for 1 to 5 percent of all instances of diabetes. MODY is a hereditary disorder that frequently appears before the age of 25(Li et al., 2015; Mack & Tomich, 2017).

2.2.5 Diabetes Secondary

Complications from other pancreatic diseases (like pancreatitis), hormone imbalances (like Cushing disease), or medications (like corticosteroids) can lead to secondary diabetes.

2.2.6 Diabetes Epidemiology

Because of the global increase in obesity and bad lifestyles, diabetes is a serious disease burden that is rising in all countries. The most recent projections indicate that by 2045, the prevalence of diabetes in Northern America and the Caribbean would increase to 13%. According to Lotfy et al. (2016) and Malek et al. (2019), the incidence rate across the Middle East and North Africa is expected to rise by 13.9% by 2045.

Africa has the lowest prevalence rate, 4.7%, which is predicted to rise to 5.2% by 2045. Incidence is frequently high or moderate in South American and South-East Asian nations. However, according to a 2019 study by Saeedi et al. (11), 463 million individuals globally have diabetes, which translates to a 9.3% global prevalence rate. The prevalence rate is predicted to reach 10.2% by 2030 and 10.9% by 2045. The region-stratified prevalence of diabetes for many countries is calculated to identify the nations with the highest number of diabetic patients in 2019 (Martos-Cabrera et al., 2020; Baker et al., 2021).

The top ten countries or territories with the highest rates of diabetes prevalence are listed. With about 116 million people, China has the highest number of diabetic sufferers. With 77 million diabetics, India comes in second, followed by the US with 31 million. This suggests that the US will be among the countries with the highest risk of developing diabetes in the coming ten years. In their high-end diabetes categories, Pakistan, Brazil, and Mexico are expected to have roughly 19 million, 16 million, and 12 million diabetic patients, respectively (Sun et al., 2021; Harrison et al., 2022). Bangladesh is at the bottom of this list, yet it is no more protected from diabetes than the US due to its growing population and a lack of well-thought-out intervention initiatives (Hussain & Chowdhury, 2019; Alam et al., 2021). The following figure shows Estimated diabetes prevalence by global region in 2019 and 2045.

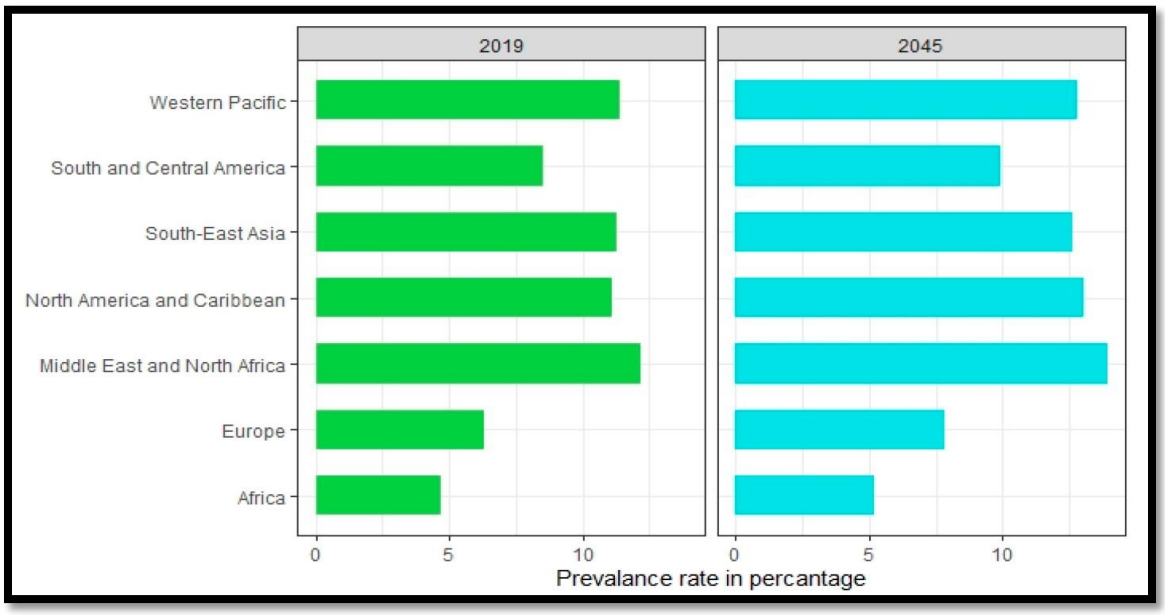

Figure 1: Estimated Diabetes Prevalence by Global Region In 2019 and 2045 (Chowdhury, 2019; Alam et al., 2021).

2.3 Diabetes Threat Factors

The public health situation has deteriorated as the prevalence of diabetes mellitus has increased globally. A variety of threat factors contribute to the complaint's occurrence. Genetics, terrain, loss of the original phase linked to insulin release, sedentary life, lack of physical exertion, smoking, alcohol consumption, dyslipidemia, decreased cell perceptivity, hyperinsulinemia, and increased glucagon exertion are the primary risk factors for prediabetes and type 2 diabetes (Barrea et al., 2023). These elements seem to be important in insulin malfunction or resistance, which advances the course of disease. Approximately 90% of people get type 2 diabetes, which is primarily brought on by obesity, according to WHO (2011). Sleep disorders and obstructive sleep apnea are common risk factors for glucose sensitivity and insulin resistance, which cumulatively lead to prediabetes and then T2DM in obese adults (Barrea et al., 2023; Katamine et al., 2023).

2.3.1 Side Effects of Various Diabetes Medications

Different diabetes drug classes have unique side effect profiles that should be considered when managing the condition clinically (Al-Farsi & Al-Maskari, 2025; Mayo Clinic, 2025). An outline of typical adverse effects linked to the main classes of diabetes medications is provided below:

• **Metformin:** Frequently results in gastrointestinal side effects like nausea, diarrhea, stomach pain, and a metallic aftertaste. Vitamin B12 deficiency may result from prolonged use. Lactic acidosis is an uncommon but dangerous risk, particularly in individuals with significantly impaired kidney function.

• **Sulfonylureas (Glimepiride, Glyburide, etc.):** May result in hypoglycemia (low blood sugar), which can cause headaches, sweating, dizziness, and confusion. Another common side effect is weight gain. Concerns have also been raised regarding elevated cardiovascular risk following myocardial infarction.

• **DPP-4 Inhibitors, such as Saxagliptin and Sitagliptin**, are generally well tolerated but can result in headaches, dizziness, upper respiratory infections, and nasopharyngitis. Rare serious side effects include acute pancreatitis and severe joint pain.

• **Side Effects of SGLT-2 Inhibitors (Canagliflozin, Dapagliflozin, etc.)** are mostly related to elevated urine glucose, which can result in genital yeast infections, UTIs, hypotension, and dehydration. Bone fractures (especially with canagliflozin) and diabetic ketoacidosis are uncommon but dangerous risks.

• **GLP-1 Receptor Agonists, such as Liraglutide and Exenatide,** frequently result in nausea, vomiting, diarrhea, and in rare cases, gallbladder disease or pancreatitis. Although they may initially cause gastrointestinal intolerance, these agents also aid in weight loss.

• **Thiazolidinediones (Tzds, Including Pioglitazone and Rosiglitazone):** Known to cause edema, weight gain, fluid retention, an elevated risk of heart failure, an increased risk of fractures, and, in the case of certain agents, concerns about cardiovascular events or bladder cancer.

• **Meglitinides, such as Repaglinide**, can lower blood sugar levels, but usually not as much as sulfonylureas. Gaining weight is another possibility.

• **Alpha-Glucosidase Inhibitors**, such as miglitol and acarbose, primarily result in gastrointestinal side effects such as bloating, gas, and diarrhea, which sometimes limit their use (Mayo Clinic, 2025).

Every drug class has different safety and tolerability issues that need to be balanced with the medication's effectiveness and patient-specific elements like comorbidities and the chance of weight gain or hypoglycemia. In the management of diabetes, appropriate monitoring and individualized treatment selection maximize benefits and reduce side effects (Al-Farsi & Al-Maskari, 2025).

2.4 Pathophysiology and Mechanisms of Type 2 Diabetes

2.4.1 Physiological and Dysfunctional Mechanisms of Insulin Secretion in T2DM β-Cell Physiology

Cells create pre-proinsulin. In the ER, pre-proinsulin changes its structure to become proinsulin. Proinsulin is transformed into insulin and C-peptide once it leaves the ER and enters the Golgi apparatus (GA). Insulin granules are held in reserve until they are released. Glucose triggers the release of insulin. Hormones, fatty acids, and amino acids can also cause the release of insulin. Glucose is absorbed into cells via the solute carrier protein glucose transporter 2 (GLUT2), which also acts as a glucose sensor. Upon entrance, the plasma membrane's ATP-dependent potassium channels close and the intracellular ATP/ADP ratio rises as glucose catabolism starts. The membrane depolarizes, allowing voltage dependent Ca2+ to (Weiskirchen & Chandrasekaran, 2024).

Channels, allowing Ca2+ to flow through. Intracellular Ca2+ primes and fuses insulin-containing granules to the plasma membrane, causing insulin exocytosis. Because of their strategic locations and ability to increase Ca2+-induced Ca2+ release (CICR), RY receptors (RYR) have the ability to amplify Ca2+ signals and may play a significant role in the stimulus-insulin secretion coupling. Ca2+ signals are increased by RYR when the channel is sensitized by ligand-binding or messenger molecules from food metabolism (Sinclair et al., 2020; Chandrasekaran & Weiskirchen, 2024).
Cells can release insulin with the aid of other cell signals. Perhaps the most important insulin-releasing messenger is cAMP. Through the depletion of intracellular Ca2+ reserves, cAMP may mobilize secretory vesicles carrying insulin. Another crucial cell regulator is extracellular ATP. Cells exocytosis insulin granules in response to glucose stimulation, producing ATP. Independent of glucose, purinergic transmission regulates insulin exocytosis and encourages Ca2+ mobilization. P2X-type receptors are ATP-activated ligand-gated ion channels non-selective for cations (Mack & Tomich, 2017; Sinclair et al., 2020).

Proteins are linked to P2Y purinoreceptors. When it comes to P2Y receptors, intracellular Ca2+ mobilization in response to IP3 synthesis may control insulin release by causing the release of Ca2+ from ER storage and enhancing the Ca2+ signal that triggers exocytosis (Sinclair et al., 2020; Chandrasekaran & Weiskirchen, 2024).

2.5 Factors Contributing to β-Cell Failure

Cell dysfunction and mortality are typically linked. Recent research suggests that a complex network of interactions between biological pathways and the environment may be the source of -cell dysfunction in type 2 diabetes. IR and chronic inflammation are exacerbated by hyperglycemia and hyperlipidemia associated with obesity. Due to their hereditary sensitivity, cells can be exposed to toxic stimuli such as amyloid stress, inflammatory stress, ER stress, and metabolic/oxidative stress, which can cause islet destruction (Broome et al., 2023; Chandrasekaran & Weiskirchen, 2024). Excess FFAs and hyperglycemia cause -cell dysfunction by causing ER stress and activating UPR pathways. Obesity-related biotoxicity, glucotoxicity, glucolipotoxicity causes metabolic and oxidative stress that damages cells.

High levels of saturated FFAs can activate the UPR pathway, which in turn can cause anxiety by blocking the sarco-endoplasmic reticulum Ca2+ ATPase (SERCA), which is responsible for ER Ca2+ mobilization, activating IP3 receptors, or directly compromising ER homeostasis (Mack & Tomich, 2017; Sinclair et al., 2020). Prolonged high blood sugar levels encourage cells to

produce proinsulin and islet amyloid polypeptides (IAAP), which leads to misfolded insulin and IAAP and raises reactive oxygen species (ROS) through oxidative protein folding reactions. These effects affect ER Ca2+ mobilization, proapoptotic signals, proinsulin mRNA degradation, and enhanced IL-1 production, which draws macrophages and worsens islet inflammation (Moon & Jang, 2022; Broome et al., 2023).

2.6 Diabetes Mellitus Management:

It was often thought that a person with diabetes would always have the disease, yet it is possible for DM to go into remission. Diabetes can be controlled by eating differently, exercising, keeping a healthy weight, keeping an eye on your lipid profile, and taking your prescription drugs as directed. One of the best ways to manage diabetes is to change your diet (Broome et al., 2021). Consuming complex carbs, protein, fiber, polyunsaturated fatty acids (PUFA), and low-glycemic index foods can help keep blood sugar levels within normal ranges. Moderate fat-loss exercise helps lower blood glucose levels by transferring glucose into the muscle through an insulin-independent process (Alam et al., 2021). One important risk factor for postpartum type 2 diabetes is GDM. Breastfeeding for three months lowers the risk of postpartum type 2 diabetes by 40%. It seems that breastfeeding enhances early postpartum glucose tolerance (PGT) (Mack & Tomich, 2017; Sinclair et al., 2020).

During lactation, fat distribution is improved, glucose and lipid metabolism are increased, and estrogen levels fall. Therefore, among women with GDM, extended lactation lowers the long-term postpartum risk of T2DM. Li et al., (2015). The last step in managing diabetes is medication. Insulin is necessary for T1DM and 25–30% of T2DM patients. Hypoglycemia, which is more dangerous than hyperglycemia, can occasionally be caused by improper insulin dosage. In order to address this problem, diabetics on insulin are often advised to carry chocolate or other sweets with them (Da Rocha et al., 2020; Dludla et al., 2020).

Patients with diabetic peripheral neuropathy (DPN) may benefit from vibration therapy. Because diabetic dyslipidemia can lead to atherosclerosis and coronary heart disease, maintaining a lipid profile is crucial to reducing the risk of these conditions. (Broome et al., 2023; Chandrasekaran & Weiskirchen, 2024). Physicians have long emphasized physical activity as a means of treating diabetes mellitus (DM), and a number of studies have shown that it is effective not just in managing diabetes but also in lowering the chance of developing age-onset diabetes and other age-onset conditions including cardiovascular disease (Sinclair et al., 2020; Chandrasekaran & Weiskirchen, 2024).

2.7 The Medication Metformin

The most used oral medication that lowers blood sugar in the majority of nations for the first-line treatment of type 2 diabetes is metformin hydrochloride, a biguanide. Galegine, a quinidine derivative present in Galega officinalis, is the source of biguanide. It is dimethyl biguanide hydrochloride in chemistry. When taken alone or in combination with other anti-diabetic medications, metformin can effectively lower HbA1c levels by 1% to 2%. Because it lowers blood glucose levels without boosting insulin secretion, it is also known as "insulin sensitizer" (Da Rocha et al., 2020; Dludla et al., 2020). Metformin can improve glycemic control, lower insulin requirements, and prevent weight gain, according to several studies. A family history of type 2 diabetes is another significant risk factor for this illness. Cardiovascular illness has been linked to early endothelial dysfunction, which is more common in healthy individuals with a family history of type 2 (Alam et al., 2021).

3. Mechanism of Action of Metformin

One drug used to treat type 2 diabetes among those who were first affected is metformin, which is a member of the biguanides family. As part of its mode of action, it lowers fasting insulin levels in the plasma, increases insulin sensitivity, improves glucose uptake in peripheral tissues, and decreases intestinal absorption of glucose. These actions result in lower glucose levels without causing significant hypoglycemia (Alam et al., 2021).

Metformin predominantly affects the liver, where it principally suppresses gluconeogenesis, the process that produces glucose, resulting in a decrease in glucose production. Additionally, it activates an enzyme known as AMP-activated protein kinase (AMPK), which reduces the liver's energy supply. By inhibiting mitochondrial respiratory chain complex 1, this activation raises NADH oxidation and, eventually, lowers ATP synthesis (energy generation) (Da Rocha et al., 2020; Dludla et al., 2020).

Compared to its effect on glycemic control alone, metformin provides more protection against the emergence of macrovascular problems and the risk of cardiovascular disease. This is because metformin improves insulin sensitivity, which lowers insulin resistance and hyperinsulinemia, which are associated with an increase in cardiovascular illnesses (Broome et al., 2023; Chandrasekaran & Weiskirchen, 2024).

Metformin has also been demonstrated to reduce cardiovascular death rates by improving adaptability of cardiomyocyte metabolism during ischemia, lowering cardiomyocyte apoptosis during ischemia, and preventing the progression of heart failure. Additionally, dyslipidemia, which is linked to a high risk of cardiovascular disease, is positively impacted by metformin as it decreases levels of free fatty acids, LDL, and TG, while increasing HDL levels, thus providing a mild beneficial impact on lipid profiles (Choi & Chung, 2016; Hussain & Chowdhury, 2019). The figure 2 shows Mechanism of action of metformin.

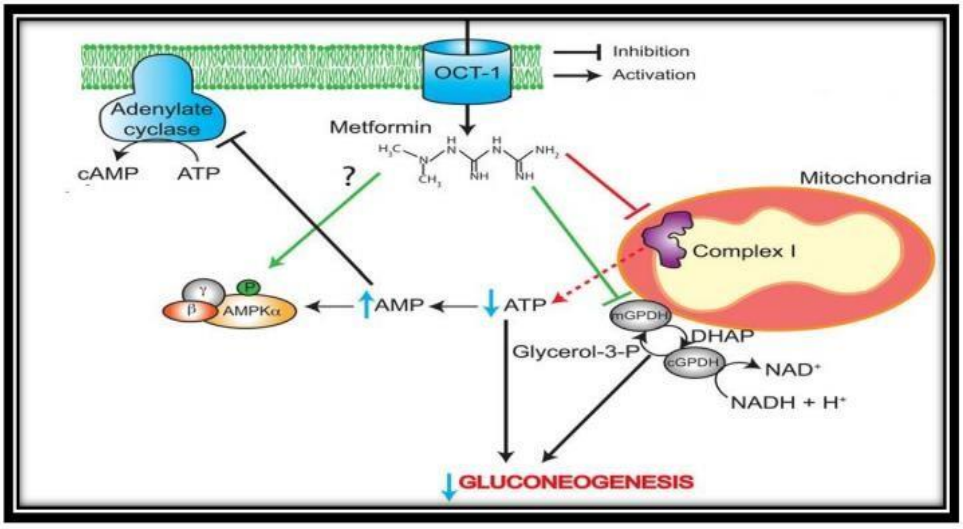

Figure 2: Mechanism of Action of Metformin (Choi & Chung, 2016; Hussain & Chowdhury, (2019).

4. Study Findings and Statistical Evidence

• Sulfonylureas: Fixed-dose combinations (e.g., glyburide/metformin) improve adherence and glycemic control.
• TZDs: Cause weight gain but have a lower risk of hypoglycemia than sulfonylureas.
• DPP-4 inhibitors: Lower risk of hypoglycemia and weight-neutral effect.
• GLP-1 agonists: Lower the risk of cardiovascular disease and encourage weight loss. Table 1 shows compare the safety and effectiveness of oral antidiabetics in combination with metformin.

Table 1: Shows Comparing the Safety and Effectiveness of Oral Antidiabetics with Metformin (Choi & Chung, 2016; Hussain & Chowdhury, 2019).

Drug Class	HbA1c Reduction	FPG Reduction	Weight Change	Hypoglycemia Risk	Benefits of Adding Metformin
Sulfonylureas Further 60-70 Gain 2-5 (Glyburide, 1.5-2%)	High	0.5-1%	A1c	reduction	less weight mg/dL kg glipizide) gain
TZDs (pioglitazone, rosiglitazone)	0.5-1.5%	30-50 mg/dL	Gain 3-5 kg	Low	Further A1c reduction, less weight gain
DPP-4 inhibitors (sitagliptin, saxagliptin)	0.5-1%	20-40 mg/dL	Neutral	Low	Further 0.3-0.7% A1c reduction
GLP-1 agonists (liraglutide, exenatide)	1-1.5%	30-60 mg/dL	Loss 1-3 kg	Low	Further A1c reduction, enhanced weight loss
SGLT2 inhibitors (canagliflozin, dapagliflozin)	0.5-1%	30-40 mg/dL	Loss 2-3 kg	Low	Further A1c reduction, enhanced weight loss
Insulin	1.5-3.5%	60-140 mg/dL	Gain 1-3 kg	High	Less insulin needed, so less weight gain and hypoglycemia

4.1 Toxicity and Side Impact Management

Hypoglycemia is one of the most common side effects of insulin. Several T2DM medicines cause the most prevalent side effect, gastrointestinal distress. Metformin should be used with caution in individuals with renal impairment and discontinued if estimated glomerular filtration rate is less than 30 mL /min, as it might cause lactic acidosis. In diabetic patients, sulfonylureas may raise the risk of cardiovascular death and induce hypoglycemia (Zheng et al., 2018; Hussain & Chowdhury, 2019; Baker et al., 2021).

Thiazolidinediones have lost favor in clinical practice because of its negative effects, which include fluid retention, an increase in heart failure, and fractures. Compared to metformin, DPP-4 may produce less nausea and diarrhea. However, it may raise the risk of upper respiratory tract infections. SGLT-2 inhibitors increase urine glucose excretion, which increases the risk of urinary tract infections. Due to increased urine glucose excretion, SGLT-2 inhibitors can increase the risk of urinary tract infections. In such patients, SGLT2 inhibitors and GLP-1 Receptor

agonists are currently considered second-line therapies after metformin (Deng & Thorn, 2022; Sweeting et al., 2022).

5. Discussion

Because of its effectiveness in reducing blood glucose levels, improving insulin sensitivity, and providing extra advantages for weight management and cardiovascular health, metformin is a mainstay in the treatment of type 2 diabetes (T2DM) (Da Rocha et al., 2020; Dludla et al., 2020). Metformin's efficacy and adaptability make it a basic treatment that, when taken alone, can have a major effect on glycemic control. However, combined medication is frequently required to achieve appropriate glycemic goals, especially when metformin alone is insufficient. In addition to improving glycemic control, the goal of combining metformin with other antidiabetic drugs is to maximize the advantages of each drug class while reducing the possibility of side effects (Chen et al., 2015; Alam et al., 2021).

According to a study, obese persons with type 2 diabetes benefit from taking insulin and metformin together in the early stages of the condition. Reductions in HbA1c, mean fasting blood glucose (MFBG), and postprandial glucose (PPG) levels were among the notable glycemic control improvements demonstrated by this combination (Da Rocha et al., 2020). Insulin and metformin therapy may be especially helpful in treating early-stage type 2 diabetes in obese individuals, since the combination therapy proved more successful than treatment with oral antidiabetic medications (sulfonylureas and metformin) alone (Sweeting et al., 2022).

In a different study, rats with diabetes caused by alloxan were given metformin and hydroxychloroquine (HCQ). When compared to the administration of glibenclamide or metformin alone, this combination, as well as the combination of glibenclamide and HCQ, demonstrated notable improvements in glycemic control (Sinclair et al., 2020). These findings suggest that HCQ could enhance the antidiabetic effects of metformin and glibenclamide, offering additional metabolic benefits. Weight reduction and insulin resistance were evaluated between the use of the weight loss drug orlistat and metformin against orlistat alone. Significant weight loss and HOMA-IR value decreases were observed in both combinations, suggesting improvements in insulin resistance (Sun et al., 2021; Katamine et al., 2023).

The fact that there was no discernible difference in the two groups' weight loss, however, indicates that in morbidly obese individuals without diabetes or prediabetes, using metformin in addition to orlistat does not offer any further weight-loss benefits (Jacobs et al., 2024). Research has also assessed the effectiveness of combining metformin with SGLT2 inhibitors (e.g., ipragliflozin) and dapagliflozin, as well as the addition of DPP-4 inhibitors (e.g., sitagliptin) to metformin and sulphonyl urea combination therapy. These pairings have been demonstrated to enhance metabolic (Jacobs et al., 2024). Metformin has been demonstrated to offer cardiovascular advantages beyond its use in combination therapy, including reducing cardiomyocyte apoptosis during ischemia, enhancing cardiomyocyte metabolic adaption during ischemia, and halting the progression of heart failure. Additionally, it improves lipid profiles by raising HDL levels and lowering LDL, triglycerides, and free fatty acid levels (Sun et al., 2021; Katamine et al., 2023).

6. Conclusion

Ultimately, a viable approach to improving treatment outcomes for type 2 diabetes is the combination of metformin with other classes of antidiabetic medications. Several pathophysiological pathways can be targeted with this strategy, enhancing glycemic control and

reducing related metabolic and cardiovascular risks. Individualized attention should be given to the patient's overall health, possible adverse effects, and the unique advantages of each drug class when choosing a combination therapy (Mayo Clinic, 2025). Finding the safest and most effective combinations as well as comprehending the long-term effects of these treatments on complications associated to diabetes should be the main goals of future study.

Study Limitations and Recommendations

This study encompassed a limited number of patients: Combination therapy with other antidiabetic medications is typically required because metformin by itself is frequently insufficient to reach appropriate glycemic objectives. Reduction Benefit: Adding metformin to orlistat does not result in any additional weight reduction benefits for morbidly obese people who do not have diabetes or prediabetes. On the other hand, recommendations of our study: Combine Insulin and Metformin: When compared to oral antidiabetic medications alone, the combination of insulin and metformin produces better glycemic results for obese people with early-stage type 2 diabetes. In addition, improve metabolic management, think about using metformin in combination with DPP-4 inhibitors (like sitagliptin) or SGLT2 inhibitors ipragliflozin and dapagliflozin.

Ethical considerations

This experiment was completed in compliance with El-Mergib University approved ethical guidelines and the Declaration of Helsinki.

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