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Review Article

A Systematic Review on Metformin

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ABSTRACT

Metformin is the major pharmacologic treatment for type II diabetes and the most recommended drug worldwide, either alone or in combination with insulin or other glucose-lowering medications. Diabetes mellitus is a collection of metabolic disorders in which the glucose concentration in the blood is higher than normal due to insufficient insulin release or improper insulin response, resulting in hypertension. For instance. Metformin has kidney protecting properties. Early detection and practical management of risk factors are essential to reducing depression and death in individuals with coronary artery disease (CAD), which is becoming more and more common worldwide. Diabetes mellitus, or DM, is thought to be a risk factor for the development of CAD. In preclinical and clinical evaluations, the diabetes medicine metformin helps reduce cardiovascular events in DM patients. Beyond its hypoglycemic effects, metformin has a preventive effect on coronary veins. Metformin provides a distinct restorative option for both necessary and optional CAD anticipation in DM and non-diabetics due to its global accessibility, course of administration, and cost. Patients with polycystic ovarian syndrome have also demonstrated notable benefits when taking metformin.

INTRODUCTION

The development of metformin began with the production of galegine-like compounds from the herb Gallega offcinalis, which has been used for centuries in Europe as a treatment to treat diabetes. They observed that there was a wide safety margin regarding metformin toxicity and that the drug's capacity to reduce blood sugar was connected with its dose-response. Since its approval in the United States in 1995 and the United Kingdom in 1958, metformin which comes in dosages ranging from 500 to 2,500 mg/day—has emerged as one of the most popular medications for the treatment of type 2 diabetic mellitus (T2DM). According to the American Diabetes Association/European Association for Study of Diabetes recommendations, it is the first line of treatment for people with type 2 diabetes. In order to lower blood glucose levels without overtly inducing hypoglycaemia, metformin reduces intestinal

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glucose absorption, improves peripheral glucose uptake, lowers fasting plasma insulin levels, and increases insulin sensitivity. Additionally, via activating AMP-activated protein kinase (AMPK), metformin can decrease gluconeogenesis. Diabetes and other metabolic disorders are largely influenced by energy metabolism, which is regulated in part by AMPK. AMPK has been shown to be necessary for preserving glucose homeostasis. Metformin has few negative side effects, but the most common ones are gastrointestinal symptoms (occurring 20%–30%), such as nausea and vomiting, and the most serious one is lactic acidosis (occurring 1/30,000), which primarily affects diabetic patients with liver and kidney problems. In theory, the drug's use has been prohibited in large groups of people with type 2 diabetes because of the risk of lactic acidosis. However, it has been shown that a small number of diabetic or at-risk people have been treated with metformin without developing an increased risk of lactic acidosis. Furthermore, some publications showing metformin's renoprotective qualities have recently been circulated.

Drug Profile: [3,15-18]

Metformin belongs to a group of medications known as biguanides. Metformin aids in regulating blood glucose (sugar) levels.

metformin

Molecular Formula: $c_4H_{12}CLN_5$

Molecular Weight: 165.62g/mol

Brands available with their dose and dosage form

Brand / Formulation	Dosage Form	Available Strengths / Dose
Metformin (generic)	Tablet (Immediate Release)	500mg, 850mg, 1000mg
Metformin (generic)	Extended-Release Tablet	500mg, 750mg, 1000mg
Riomet	Oral Solution	100mg/ml (i.e., 500mg/5ml)
Riomet ER	Extended-Release Suspension	Reconstituted; 500mg/ml; bottle: 47.31g/473ml
Glucophage XR	Extended-Release Tablet	Common ER from (strengths similar to generic ER)
Fortamet	Extended-Release Tablet	Brand-name ER, strengths like 500mg, 1000mg

IUPAC name: N,N-Dimethylimidodicarbonimidic diamide

Physical properties of metformin:

- Nature: White, hygroscopic crystalline powder
- Solubility: Freely soluble in water

Slightly soluble in Ethanol

Insoluble in acetone, ether or chloroform

- Melting Point: 222-226^{0}C

Dissociation Constant(pKa): 12.4.

log(P): -2.6

Mechanism Of Action: [19-20] Diabetes that is not insulin-dependent and does not improve with dietary changes is treated with metformin. As a metabolic inhibitor, metformin modifies how cellular energy is metabolized throughout the body.

Hepatic gluconeogenesis inhibition is its primary mode of action in the illness. Metformin lowers cellular ATP levels and causes a buildup of AMP by interacting with complex 1 of the mitochondrial electron transport chain. AMPc-PKA signalling is disrupted when AMP binds to the adenylate cyclase site, inhibiting its response to glucagon. Consequently, glycolysis is promoted and the gluconeogenic pathway enzymes' activity is suppressed. The process is most likely the primary way that metformin lowers the amount of glucose produced by the liver.

Physicochemical Properties: [20-24]

N, N-dimethylimidodicarbonidediamide hydrochloride is the chemical name for metformin hydrochloride, a white or almost white crystal. Its CAS number is 1115-70-4, and its chemical formula is $C_4H_{11}N_5$.HCl. The molecular mass of metformin hydrochloride is 165.6 g/mol, while that of metformin itself is 129.16 g/mol. It is essentially insoluble in acetone and methylene chloride, somewhat soluble in alcohol, and easily soluble in water when hydrochlorided (1.38 mg/ml).21 Its pKa is 12.4 (basic), its LogP is -0.5, and its melting point is between 223 and 226^0 C.

Disease:

Diabetes Mellitus: [25-29] The medication metformin is mostly used to treat type II diabetes mellitus, particularly in obese people. When compared to insulin, glibenclamide, and chlorpropamide, the medication metformin has been shown to cause approximately one-third of deaths and complications in diabetics.

Without raising insulin release, metformin lowers serum glucose levels by a number distinct mechanisms, most notably through non-pancreatic systems. The impacts of insulin are built; subsequently, it is known as “sensitizer of insulin.” Metformin also inhibits the liver's ability to produce glucose, primarily due to a slowdown in gluconeogenesis and a minimal effect on glycogenolysis. Additionally, metformin activates insulin flagging and glucose transport in muscle cells while inhibiting key proteins involved in gluconeogenesis and glycogen combination in hepatocytes through the action of the chemical adenosine monophosphate kinase. AMPK controls the breakdown of organs and the reduction of hepatocyte energy, which causes AMPK activation. This review has made some progress in explaining how metformin migration affects hepatocyte gluconeogenesis. Additionally, metformin creates the peripheral glucose ejection that frequently results from prolonged non-oxidative glucose absorption into voluntary muscles. It is often regarded as a formidable foe of diabetes medications because it does not lower blood glucose levels. Compared to insulin and sulfonylureas, metformin treatment for diabetes is associated with less weight gain. In cases of weight increase, glucose is better managed. According to a review, patients receiving metformin gained around 1 kg, those receiving glibenclamide gained about 3 kg, and those receiving insulin gained about 6 kg over the course of 10 years of treatment.

Cardiovascular Protective Effects of Metformin: [3,30-44] Heart and brain macrovascular diseases account for about 70% of the deaths of diabetic patients. Cardiovascular complications include microvascular problems like kidney disease, retinal damage, and peripheral nerve disease, as well as macrovascular problems like myocardial infraction, coronary artery disease [CAD], and stroke. Metformin lowers the incidence and mortality of cardiovascular events and provides cardiovascular preventive benefits, according to several clinical investigations. The first trial to establish that metformin could

significantly lower the incidence of acute myocardial infarction and all-cause mortality in overweight patients with type 2 diabetes was the UKPDS, a randomized, prospective multicenter trial conducted in 1998.

Metformin's cardiovascular protective properties.	850 mg once daily at first, then 850 mg twice daily, and finally 1700 mg. 850 mg in the morning and 850 mg with the evening meal (maximum dose = 2500 mg). 1.4+_0.2g.

Furthermore, a 10-year follow-up of the UKPDS survivor cohort investigated the long-term benefits of metformin medication on cardiovascular risk in individuals who were overweight. Treatment with metformin can effectively lower the risk of myocardial infraction and death when compared to sulfonylurea and insulin. Roumi et al. also shown that metformin medication was linked to a lower risk of cardiovascular disease events or death in individuals with type 2 diabetes when compared to sulfonylurea therapy. Furthermore, the use of metformin as a supplementary preventive strategy was linked to a 24% decrease in all-cause mortality among patients with atherothrombosis following a 2-year follow-up, according to data from the reduction of atherothrombosis for Continued Health Registry. Therefore, metformin's cardiovascular-protective effects are distinct from its effects on reducing blood sugar levels. Furthermore, Hong et al. discovered in a multicenter, randomized, double-blind, placebo-controlled clinical trial that metformin treatment for three years (mean daily dose was 1.4+_0.2g) significantly decreased major cardiovascular events in a median follow-up of five years among type 2 diabetic patients with CAD when compared to glipizide. This suggested that metformin treatment may have a positive impact on cardiovascular outcomes in high-risk patients. After all, the 2013 AACE guidelines recommend metformin as the only antidiabetic medication for cardiovascular benefit. It's possible that metformin can help avoid heart disease. Among the risk factors for cardiovascular disease include insulin resistance, obesity, hypertension, and dyslipidemia. First, by activating AMPK, metformin may enhance lipometabolism and lower LDL cholesterol levels. Second, metformin was linked to either weight gain or loss; the mechanism is believed to be that a reduced sense of hunger leads to a decrease in food consumption. Third, a recent meta-analysis revealed that metformin may successfully lower systolic blood pressure in individuals without diabetes. The medication may lower blood pressure through a number of mechanisms, such as decreasing insulin resistance and plasma insulin, deactivating adrenergic receptors, lowering intracytoplasmic calcium, inhibiting sympathetic drive, particularly when dietary salt intake is high, and increasing glomerular filtration rate and sodium excretion. Furthermore, metformin can enhance endothelial cell function and reduce oxidative stress and inflammation.

Poly-Cystic Ovarian Syndrome: [45-53] Insulin resistance is frequently linked to polycystic ovarian syndrome, and metformin was introduced as a therapy for PCOS (polycystic ovarian syndrome) in 1994. When several treatments don't work, the National Institute for Health and Clinical Excellence recommended metformin in 2004 for females with polycystic ovarian syndrome and index of body mass over 25 for cases of infertility and anovulation. However, aside from females with glucose intolerance, a few subsequent audits did not reveal encouraging results and did not recommend it further or perhaps as a first-line drug. Generally speaking, the guidelines recommend clomiphene as the main treatment and a lifestyle shift separate from medication therapy.

For infertile instances, an organized survey using relative preliminary treatments such as metformin clomiphene found comparable results. According to a BMJ article, metformin should be used as a backup plan regardless of whether clomiphene treatment fails. Furthermore, a massive audit using twenty-seven clinical preliminary results found that metformin was not associated with an increase in the number of live births; nevertheless, it did increase ovulation rates, primarily when combined with and used with clomiphene.

According to an audit, metformin is the best choice because it has positive effects on weight, hirsutism, anovulatory instances, insulin blockage, and many of these conditions are frequently linked to polycystic ovarian syndrome.

Various initial plans could be the cause of the troublesome results. For example, using the rate of live delivery as the outcome instead of pregnancy would have skewed a few preliminary findings against metformin. According to many explanations, the effectiveness of metformin may vary depending on the population.

Lactic Acidosis: [54-76] Lactic acidosis cases in people on metformin are continuously being reported. In one investigation, twenty fatal cases of lactic acidosis were reported among one million patients. 43 of the individuals under observation had renal issues (a significant contraindication to metformin) or additional risk factors for lactic acidosis besides metformin (basically, cardiovascular collapse from congestive causes). Patients with metformin-related lactic acidosis have a mortality rate that appears to be associated with cardiovascular breakdown and is approximately 40%.

Additional evidence of large metformin-related lactic acidosis cases, particularly fatal forms linked to hidden diseases rather than metformin, is provided by a recent Stadesetal audit. The authors attributed a number of findings regarding lactic acidosis associated with metformin to a distribution tendency that incorrectly reinforces the widely accepted tested impression that metformin causes lactic acidosis.

In non-diabetic patients, lactic acidosis is associated with malignant growth, liver problems, kidney failure, and frequently a death harbinger, unless the concealed circumstance is corrected. The rate of lactic acidosis in victims with type I diabetes should be comparable for both patients taking metformin and those who have never taken it.

According to Stacpoole, "responsibility by relationship" and phenformin should be addressed in cases involving metformin-related lactic acidosis. Stades et al. attributed a number of metformin-related lactic acidosis instances to the fact that diabetic patients are more likely to develop actual conditions that result in lactic acidosis. Furthermore, the lack of correlation between victims' lactate and metformin levels clearly suggests that metformin is often a blameless spectator. If one considers how metformin is used, there aren't many documented cases of lactic acidosis linked to the medication. As evidence that metformin is not causing lactic acidosis, it has been used safely in patients who experienced severe side effects. However, reports of metformin producing lactic acidosis, particularly in children without any risk factors, suggest that metformin can cause lactic acidosis when taken in large doses.

It is rare, if at all, for metformin to cause lactic acidosis when taken as prescribed. In patients with conditions that can cause lactic acidosis on their own (cardiovascular collapse, low oxygen, sepsis, etc.), metformin is linked to lactic acidosis. Regardless, it is hard to say how much, if any,

metformin might contribute to the progression of lactic acidosis. The increased risk of developing lactic acidosis is negligible when metformin is used as prescribed. Otherwise, they are close to zero, making it impossible to include in the standard clinical dynamic. Lactic acidosis, which is caused by metformin, is maintained by the person who has taken gluts. In order to guarantee that victims are in danger, it may be necessary to accumulate metformin in order to prepare kidney inadequacy, which will promote lactic acidosis. The majority of cases of metformin-related lactic acidosis, particularly fatal forms, were probably not caused by the medication if one avoids taking excessive amounts of glucose.

Metformin Uses:

- Metformin mainly used to treat hyperglycemia caused by a type of diabetes mellitus
- Other uses of metformin:

Its being used off-label to treat:

- ✓ Weight reduction
- ✓ Polycystic ovarian syndrome (PCOS)
- ✓ Infertility
- ✓ Prevention of Obesity
- ✓ Prevention of diabetes, pregnancy complications

Side effects of metformin: The most frequent side effect of metformin is stomach problems. Roughly 25% of people struggle with issues like:

- Diarrhoea
- Loss of appetite
- Stomach ache
- Metallic taste in mouth
- Nausea and vomiting
- Lactic acidosis
- Flatulence
- Asthenia

Rare side effects of metformin:

After using extended-release metformin, a tiny percentage of participants (less than 5% in one study) reported headaches, upper respiratory infections, heartburn, or a foul taste in their mouth. Up to 12% of consumers had those adverse effects when using the standard recipe. Along with flu-like symptoms, they also reported flushing, sweating, heart palpitations, rashes, and nail problems.

The dangerous condition that arises from your muscles and red blood cells producing lactic acid naturally is lactic acid buildup. Metformin-associated lactic acidosis (MALA) is the term for this condition that develops when taking the medication.

The problem is incredibly rare, affecting only a tiny portion of drug users.
It usually happens when you have liver or kidney problems, drink excessively, have extremely severe heart failure from congestion, have a fever, vomiting, or diarrheal illness, or don't drink enough water.

It occurs mostly when you:

- Possess liver or kidney disease
- Consume copious amounts of alcohol

- Extremely severe cardiac failure from congestion
- Have a fever, diarrhoea, or vomiting illness
- Lack fluids
- Many of the warning signs, such as weakness, nausea, and vertigo, are similar to the side effects of metformin. Additional symptoms include cold or numbness in the limbs and variations in heart rate.

Contraindications:

The following conditions should prevent metformin use:

- Significant renal impairment (eGFR <30 mL/1.73 m2)Metabolic acidosis, either acute or chronic, with or without coma, including diabetic ketoacidosis (caused by uncontrolled diabetes).
- Hypertensive to metformin by known

Drug interactions:

Cationic Drugs	have the potential to possibly interact with metformin by competing for the same renal tubular processes.
Carbonic anhydrase inhibitors	Reduce serum bicarbonate levels often to avoid non-anion gap and hyperchloremic metabolic acidosis.
Drugs affecting glycemic control	These include isoniazid, corticosteroids, phenytoin,nicotinic acid, sympathomimetics, calcium channel blockers, thyroid products, estrogens, thiazides, and other diuretics.

Safety:

Metformin is among the safest oral hypoglycemic drugs. Because it doesn't increase B-cell insulin production, it reduces insulin resistance without raising the risk of hypoglycemia.

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