



Different Combinations of Metformin with Other Oral Hypoglycemic Agents

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ABSTRACT

The present review article introduces about diabetes disease type, symptoms, medication. In which especially focus on Metformin, which is widely use medicine but because of its serious adverse effect like, Lactic acidosis. As a result, combination therapy can be a good option for it.

Keywords: Diabetes, Metformin, Lactic acidosis, Drug combination.

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INTRODUCTION

Diabetes is a chronic disease that occurs because the body is unable to use blood sugar (Glucose) properly. In that condition blood sugar is too high. Blood glucose is main source of energy and comes from food you eat. Insulin, a hormone made by the pancreas, helps glucose from food get into your cells to be used for energy. Sometimes your body doesn't make enough insulin or doesn't use insulin well. Glucose then stays in your blood and doesn't reach your cells. This problem is called as Diabetes. Untreated high blood sugar from diabetes can damage your nerves, eyes, kidneys, and other organs.¹

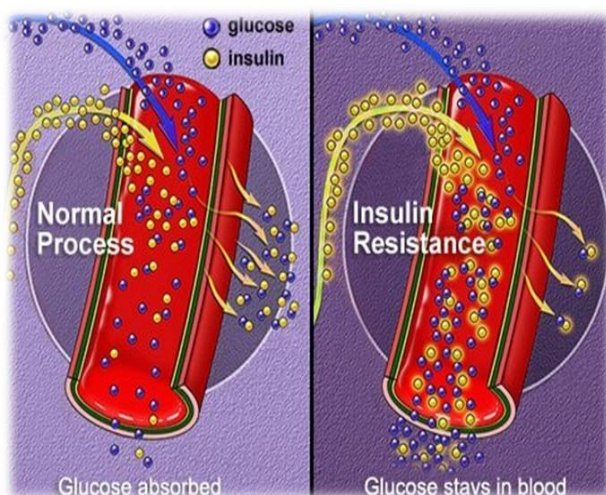


Figure 1: Glucose absorption level

Classification of diabetes mellitus

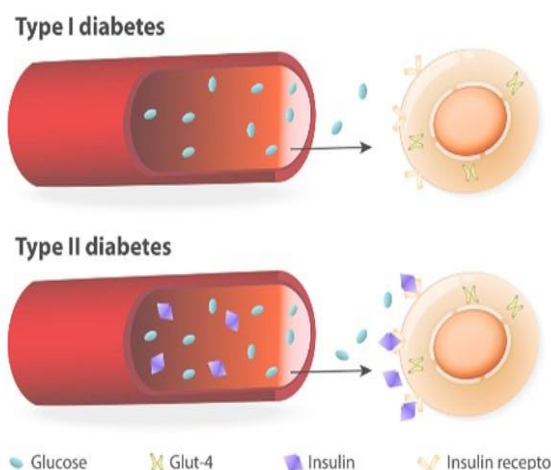


FIGURE 2: Type-1 and Type-2⁴

Diabetes can be classified into the following general categories:

Type 1 Diabetes

- Type 1 diabetes is a chronic disease. It is also called insulin-dependent diabetes. It used to be called juvenile-onset diabetes, because it often begins in childhood.
- Immune system mistakenly attacks and destroys insulin-producing beta cells in the pancreas. In people with type 1 diabetes, cells in the pancreas that make insulin are destroyed, and the body is unable to make insulin.
- Insulin is a hormone that helps your body's cells use glucose for energy. Your body gets glucose from the food you eat. Insulin allows the glucose to pass from your blood into your body's cells.
- When the cells have enough, your liver and muscle tissues store the extra glucose, also called blood sugar, in the form of glycogen.

- It's broken down into blood sugar and released when you need energy between meals, during exercise, or while you sleep.
- In type 1 diabetes, the body is unable to process glucose, due to the lack of insulin.
- Glucose from your food can't make its way into the cells. This leaves too much glucose circulating in your blood.
- High blood sugar levels can lead to both short-term and long-term problems.^{3,15}

Symptoms of type 1 diabetes can include:

- ❖ extreme hunger
- ❖ increased thirst
- ❖ unintentional weight loss
- ❖ frequent urination
- ❖ blurry vision
- ❖ tiredness
- ❖ It may also result in mood changes.⁶

A person might also develop ketoacidosis, a complication of diabetes. Symptoms of this condition include:

- rapid breathing
- dry skin and mouth
- flushed face
- nausea
- vomiting or stomach pain¹⁵

Type 2 diabetes

- Type 2 diabetes starts as insulin resistance. This means your body can't use insulin efficiently. That stimulates your pancreas to produce more insulin until it can no longer keep up with demand.
- Insulin production decreases, which leads to high blood sugar. People who are middle-aged or older are most likely to get this kind of diabetes, so it used to be called adult-onset diabetes.
- But type 2 diabetes also affects kids and teens, mainly because of childhood obesity.

The exact cause of type 2 diabetes is unknown. Contributing factors may include:

- Genetics
- age 45 or older
- aren't physically active
- have had gestational diabetes
- have prediabetes

- have high blood pressure
- high cholesterol
- lack of exercise
- being overweight¹⁶

Symptoms of type 2 diabetes can include:

- increased hunger
- increased thirst
- increased urination
- blurry vision
- tiredness
- sores that are slow to heal
- It may also cause recurring infections. This is because elevated glucose levels make it harder for the body to heal.⁶

Type 1 vs. type 2 diabetes

- There are two main types of diabetes: type 1 and type 2. They have similar symptoms, and over time, they can lead to many of the same complications. However, they are very different diseases.
- Type 1 diabetes is the result of the body not producing insulin on its own. Taking insulin is necessary for survival, to move glucose from the bloodstream into the body's cells.
- For people with type 2 diabetes, the cells have stopped responding well to insulin. The body struggles to move glucose from the blood into the cells, despite adequate levels of the hormone. Eventually, their bodies may stop making adequate insulin entirely.
- Type 1 diabetes develops very quickly, and symptoms are obvious. For people with type 2 diabetes, the condition can develop over many years. In fact, a person with type 2 diabetes may not know they have it until they have a complication.
- The two types of diabetes are caused by different things. They also have unique risk factors.¹⁴

Common Symptoms of Diabetes mellitus

- ❖ Polyuria (excessive urination)
- ❖ Polydipsia (excess thirst)
- ❖ Polyphagia (excessive eating OR Appetite)
- ❖ Weakness
- ❖ Fatigue
- ❖ Weight loss
- ❖ Blurred vision⁵



Medication

There are various classes available for diabetes mellitus.

- **Sulfonylureas** (glipizide, glyburide, gliclazide, glimepiride)
- **Meglitinides** (repaglinide and nateglinide)
- **Biguanides** (metformin)
- **Thiazolidinediones** (rosiglitazone, pioglitazone)
- **α -Glucosidase inhibitors** (acarbose, miglitol, voglibose)

They all are using in the treatment of diabetes mellitus with some serious side effects.

Potential side effects of common diabetes drugs

Sulfonylureas

Low blood sugar, upset stomach, skin rash or itching, weight gain

Biguanides/Metformin

Sickness with alcohol, kidney complications, upset stomach, tiredness or dizziness, metal taste

Alpha-glucosidase inhibitors

Gas, bloating and diarrhoea

Thiazolidinediones

Weight gain, risk of liver disease, anaemia risk, swelling of legs or ankles,

Meglitinides

Weight gain, low blood sugar⁷

- All these drugs having their side effects but some effects are serious and harmful for human body like, thiazolidines having risk of liver disease. While some drugs do not cause serious problems however, less able to cure the disease properly that's also not good for our health because if our disease is not cure properly by medication then disease level will increase more and more in our body.
- As a solution combination of different medication can cure the disease with less side effects.
- Generally other class drugs are combined with Metformin. Because of more efficacy and minor side effects.

Metformin

- Metformin is generally well tolerated and it having less side effects. Metformin was discovered in 1922. French physician Jean Sterne began study in humans in the 1950s. It was introduced as a medication in France in 1957 and the United States in 1995.
- It is on the World Health Organization's list of essential medicines. Metformin is the most widely used medication for diabetes taken by mouth.

- It is available as a generic medication in 2017, it was the fourth-most commonly prescribed medication in the United States, with more than 78 million prescriptions.
- Metformin is an oral antidiabetic agent, widely use in the treatment of type 2 diabetes mellitus. Metformin lowers the blood glucose concentration. It is a common first-line treatment for type 2 diabetes.
- It helps reduce your blood sugar levels, can lower your risk of cardiovascular events like heart attack, and has a low risk of causing harmful drug interactions and severe side effects.⁸

Why Metformin

- Metformin having more beneficial in diabetes mellitus than other medication like, it is affordable in cost with minimum side effects metformin has become the first-line therapy for patients with type 2 diabetes.¹³
- Metformin helps to control the amount of glucose (sugar) in your blood. It decreases the amount of glucose you absorb from your food and the amount of glucose made by your liver. Metformin also increases your body's response to insulin, a natural substance that controls the amount of glucose in the blood.¹⁰

Side effects of Metformin

- Nausea
- Vomiting
- Abdominal pain
- Stomach pain
- Diarrhoea
- Constipation
- Gas⁹

These all are common side effects of Metformin but that medication having one serious side effect which is lactic acidosis and its dangerous for our body.

Lactic acidosis is a medical condition characterized by the build-up of lactate (especially L-lactate) in the body, with formation of an excessively low pH in the bloodstream.

It is a form of metabolic acidosis, in which excessive acid accumulates due to a problem with the body's oxidative metabolism. when lactic acid starts to build up it is called the "lactate threshold."

Some common symptoms of lactic acidosis are, Muscle ache, burning, rapid breathing, nausea, stomach pain. If we feel that types of symptoms while taking Metformin then it's lactic acidosis. While sometimes it causes some other serious medical condition.¹¹

Some medical conditions can also bring on lactic acidosis, including:

- Cancer



- Seizures
- Liver failure
- Vitamin B deficiency
- Sepsis (a whole-body inflammation caused by severe infection)
- Shock¹²

To resolve this problem, combination therapy can be used.

Metformin Combination with Other Oral Hypo Glycaemic Agents

Metformin + Glyburide

Glyburide and metformin combination is used to treat a type of diabetes mellitus called type 2 diabetes. It is used together with a proper diet and exercise to help control blood sugar levels.

Glyburide causes your pancreas to release more insulin into the bloodstream. Metformin reduces the absorption of sugar from the stomach, reduces the release of stored sugar from the liver, and helps your body use sugar better¹⁸.

Uses

This combination medication is used with a proper diet and exercise program to control high blood sugar in people with type 2 diabetes. It may also be used with other diabetes medications.

This product contains 2 medications. Glyburide belongs to the class of drugs known as sulfonylureas. It lowers blood sugar by causing the release of your body's natural insulin and by decreasing the amount of sugar that your liver makes. Metformin works by decreasing the amount of sugar that your liver makes and that your stomach/intestines absorb. Both of these medications work by helping to restore your body's proper response to the insulin you naturally produce.

Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems. Proper control of diabetes may also lessen your risk of a heart attack or stroke.

How to use Glyburide-Metformin HCL

Take this medication by mouth with meals as directed by your doctor, usually once or twice a day. Drink plenty of fluids while taking this medication unless otherwise directed by your doctor.

The dosage is based on your medical condition and response to treatment. To reduce your risk of side effects (such as upset stomach and low blood sugar), your doctor may direct you to start this medication at a low dose and gradually increase your dose. Your doctor will adjust your dose based on your blood sugar to find the best dose for you. Follow your doctor's instructions carefully.

If you are already taking another diabetes drug (such as chlorpropamide), follow your doctor's directions carefully for stopping the old drug and starting this combination medication.

If you are also taking colesevelam, take glyburide/metformin at least 4 hours before colesevelam.

Use this medication regularly to get the most benefit from it. To help you remember, take it at the same time(s) each day.

It may take up to 2 weeks before you get the full benefit of this drug. Tell your doctor if your condition does not improve or if it worsens (your blood sugar is too high or too low).

Side Effects

- Nausea
- stomach upset
- diarrhoea
- weight gain¹⁹

Metformin + Glipizide

What is glipizide and metformin (metaglip)?

Glipizide and metformin are combination of two oral diabetes medicines that help control blood sugar levels.

Glipizide and metformin is used together with diet and exercise to improve blood sugar control in adults with type 2 diabetes. This medicine is not for treating type 1 diabetes.²⁰

Uses

This diabetes medication is a combination of 2 drugs (glipizide and metformin). It is used along with a diet and exercise program to control high blood sugar in patients with type 2 diabetes.

Glipizide is a sulfonylurea and works by stimulating the release of your body's natural insulin and by decreasing the amount of sugar that your liver makes.

Metformin is a biguanide and works by decreasing the amount of sugar that your liver makes and that your stomach/intestines absorb. Both of these medications work by helping to restore your body's proper response to the insulin you naturally produce.

Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems. Proper control of diabetes may also lessen your risk of a heart attack or stroke.

How to use Glipizide-Metformin

Take this medication by mouth, usually once or twice a day with meals or as directed by your doctor. Drink plenty of fluids while taking this medication unless otherwise directed by your doctor.



The dosage is based on your medical condition, response to treatment, and other medications you may be taking. Be sure to tell your doctor and pharmacist about all the products you use (including prescription drugs, non-prescription drugs, and herbal products). To reduce your risk of side effects (such as upset stomach)¹⁷

Common side effects may include

- upset stomach
- nausea
- Diarrhoea
- headache
- cold symptoms such as stuffy nose, sneezing, sore throat.²⁰

Metformin + Pioglitazone

Pioglitazone belongs to a class of drugs known as thiazolidinediones or "glitazones". Metformin and pioglitazone work by helping to restore your body's proper response to the insulin you naturally produce. Metformin also decreases the amount of sugar that your liver makes and that your stomach/intestines absorb.

This combination medication is used along with a proper diet and exercise program to control high blood sugar in people with type 2 diabetes.

Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems.

Proper control of diabetes may also lessen your risk of a heart attack or stroke.

How to use Pioglitazone-Metformin

Take this medication by mouth as directed by your doctor, usually once or twice daily with meals to decrease stomach upset. Drink plenty of fluids while taking this medication.

The dosage is based on your medical condition, response to treatment, and other medications you may be taking.

Be sure to tell your doctor and pharmacist about all the products you use (including prescription drugs, non-prescription drugs, and herbal products). To reduce your risk of side effects (such as upset stomach), your doctor may direct you to start this medication at a low dose and gradually increase your dose.

Take this medication regularly in order to get the most benefit from it. Remember to use it at the same time(s) each day.

If you are already taking another diabetes medication, follow your doctor's directions carefully for stopping/continuing the old drug and starting this medication.

Side Effects

- Nausea, vomiting
- stomach upset, diarrhoea

- weakness
- sore throat
- muscle pain
- weight gain

Metformin + Rosiglitazone

Most antidiabetic agents target only 1 of several underlying causes of diabetes. The complementary actions of the antidiabetic agent's metformin hydrochloride and rosiglitazone maleate may maintain optimal glycaemic control in patients with type 2 diabetes; therefore, their combined use may be indicated for patients whose diabetes is poorly controlled by metformin alone.

How it works

Rosiglitazone maleate is an oral antidiabetic agent, which acts primarily by increasing insulin sensitivity. Rosiglitazone improves glycaemic control while reducing circulating insulin levels.

Metformin + Tenueligliptin

Tenueligliptin is used for the treatment of type 2 diabetes mellitus.

It belongs to a group of medics.

Uses

Tenueligliptin is used for the treatment of type 2 diabetes mellitus.

It works by increasing the amount of insulin released by the pancreas, which helps lower the blood glucose levels in the body²⁵.

Common side effects

Tenueligliptin includes,

- headache
- hypoglycaemia in combination with insulin sulphonyl urea
- nausea, vomiting
- nasopharyngitis
- stomach pain
- upper respiratory tract infections.²¹

Metformin + Insulin

Metformin improves glycaemic control in poorly controlled type 2 diabetic patients. Its effect in type 2 diabetic patients who are intensively treated with insulin has not been studied.

A total of 390 patients whose type 2 diabetes was controlled with insulin therapy completed a randomized controlled double-blind trial with a planned interim analysis after 16 weeks of treatment.



The subjects were selected from three outpatient clinics in regional hospitals and were randomly assigned to either the placebo or metformin group, in addition to insulin therapy.

Intensive glucose monitoring with immediate insulin adjustments according to strict guidelines was conducted.

Indexes of glycaemic control, insulin requirements, body weight, blood pressure, plasma lipids, hypoglycemic events, and other adverse events

In type 2 diabetic patients who are intensively treated with insulin, the combination of insulin and metformin results in superior glycaemic control compared with insulin therapy alone, while insulin requirements and weight gain are less.^{22,24}

How it works

When Metformin is added to insulin therapy, insulin requirements are likely to decrease. Although one would anticipate benefits from reduction in circulating insulin concentrations, the studies do not provide data to determine if benefits of combination therapy outweigh risks.²³

Medical condition while we can't take Metformin

- ❖ Over 65 years old
- ❖ If you have ever had a heart attack
- ❖ Stroke
- ❖ Diabetic ketoacidosis (blood sugar that is high enough to cause severe symptoms and requires emergency medical treatment)
- ❖ A coma
- ❖ Heart disease
- ❖ Liver disease

In that type of serious conditions, you can't take Metformin as medication. It causes more complication with your condition.

Other possible benefits of Metformin

- ✚ Most people with type 2 diabetes tolerate metformin well and are glad it's available in generic form, which keeps the price low. The medication is so effective as a first-line therapy. But metformin could have additional uses and benefits outside of treating type 2 diabetes.
- ✚ Researchers are currently studying whether the medicine can help in the fight against cancer, neurodegenerative conditions, vision problems like macular degeneration, and even aging. It will be a while, however, before uses other than blood-glucose lowering is proven to be effective.
- ✚ At the same time, metformin is also used in the treatment of gestational diabetes and polycystic ovary syndrome.¹³

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