

Combination Therapy in Diabetes: Review

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ABSTRACT

Diabetes is a disorder of metabolism—the way the body uses digested food for growth and energy. Most of the food people eat is broken down into glucose, the form of sugar in the blood. Glucose is the main source of fuel for the body. Diabetes is associated with β cell failure. There are 2 types of diabetes i.e type 1 diabetes and type 2 diabetes. The other type is gestational diabetes. In type 1 diabetes the body does not produce insulin. Some people may refer to this type as insulin dependent diabetes juvenile diabetes, or early – onset diabetes. In type 2 Diabetes the body does not produce enough insulin for proper function, or the cells in the body do not react to insulin (insulin resistance). Gestational diabetes occurs in pregnant women. Common symptoms of diabetes:- Urinating often, Feeling very thirsty, Feeling very hungry, Extreme fatigue , Blurry vision , Weight loss. Antidiabetic combinations are medicines with two or more classes of antidiabetic agents (with different mechanisms of action) in one pill or dose. Just having one pill may improve compliance and better glycemic control. Monotherapy often fails after a period of treatment, so that multiple drugs are needed to achieve effective glycemic control. Advantages of using combination drug therapy in diabetes are better glycemic control with 2 drugs that work at different sites, fewer side effects with lower doses of 2 drugs than a large dose of 1 drug, when combined in the same pill or capsule, the likelihood of patient adherence to therapy may increase and the cost may be lower, depending on the agent. Review includes combination of insulin with Sulfonylurea, Metformin, Acarbose and Troglitazone, combination of metformin with Repaglinide and Sitagliptin, and combination therapy with Dapaglifozin.

Keywords: Diabetes, Combination therapy, Insulin, Antidiabetic combination, Metformin, Insulin.

INTRODUCTION

Diabetes is a disorder of metabolism—the way the body uses digested food for growth and energy. Most of the food people eat is broken down into glucose, the form of sugar in the blood. Glucose is the main source of fuel for the body.¹ After digestion, glucose passes into the bloodstream, where it is used by cells for growth and energy. For glucose to get into cells, insulin must be present. Insulin is a hormone produced by the pancreas, a large gland behind the stomach.¹ Diabetes is associated with β cell failure³. When people eat, the pancreas automatically produces the right amount of insulin to move glucose from blood into the cells. In people with diabetes, however, the pancreas either produces little or no insulin, or the cells do not respond appropriately to the insulin that is produced. Glucose builds up in the blood, overflows into the urine, and passes out of the body in the urine. Thus, the body loses its main source of fuel even though the blood contains large amounts of glucose.¹

Types of diabetes

Type 1 diabetes

The body does not produce insulin. Some people may refer to this type as insulin dependent diabetes juvenile diabetes, or early– onset diabetes. People usually develop type 1 diabetes before their 40th year often in early adulthood or teenage years. Type 1 diabetes is nowhere near as common as type 2 diabetes. Approximately 10% of all diabetes cases are type 1.² Patient with type 1 diabetes will need to take insulin injection for the rest of their life. They must also ensure proper blood glucose level by carrying out regular blood tests.²

Type 2 Diabetes

The most common form of diabetes is type 2 diabetes. About 90 to 95 percent of people with diabetes have type 2.¹ This form of diabetes is most often associated with older age, obesity, family history of diabetes, previous history of gestational diabetes, physical inactivity, and certain ethnicities.¹ The

body does not produce enough insulin for proper function, or the cells in the body do not react to insulin (insulin resistance).² Drinking just one can of (non-diet) soda per day can

raise our risk of developing type 2 diabetes by 22%.² Men whose testosterone levels are low have been found to have a higher risk of developing type -2 diabetes.²

	Normal	Diabetes
Fasting blood sugar	80-99 mg/dl	126 mg/dl and above
Random blood sugar	80-139 mg/dl	200 mg/dl and above
2 hr glucose tolerance test	80-139 mg/dl	200 mg/dl and above

Gestational diabetes

Gestational diabetes occurs in pregnant women who have never had diabetes before but who have high blood sugar levels during pregnancy. Gestational diabetes affects about 4% of all pregnant women. After childbirth the mother may go on to develop type 2 diabetes.⁴ As with type 2 diabetes, gestational diabetes occurs more often in some ethnic groups and among women with a family history of diabetes. Gestational diabetes is caused by the hormones of pregnancy or a shortage of insulin. Women with gestational diabetes may not experience any symptoms.¹

Symptoms of diabetes^{5,6}

Common symptoms of diabetes:

- Urinating often
- Feeling very thirsty
- Feeling very hungry - even though you are eating
- Extreme fatigue
- Blurry vision
- Cuts/bruises that are slow to heal
- Weight loss - even though you are eating more (type 1)
- Tingling, pain, or numbness in the hands/feet (type 2).
- Slow healing cuts and erectile dysfunction.

Why diabetes symptoms are developing?⁸

What is glucose homeostasis? Human homeostasis means a stable condition throughout the body. The body is carrying out various complex interactions to keep a proper healthy range. Maintaining blood glucose within the normal range is glucose homeostasis. If there is, any disturbance to this glucose homeostasis will lead to various bodily symptoms.

• Why are diabetics, pee often and in large quantities?

If the blood-sugar level get elevated and your body cells are unable to consume it. Then, these high-sugar level remains, until the kidney flush out this extra sugar in blood as urine (pee). Therefore, people with diabetes

urinate frequently and/or in large quantities, urine often contains sugar, and other minerals (such as sodium, chloride, potassium, and bicarbonate).

•Why diabetics are having severe frequent Thirst?

The human body needs water to keep enough blood and other fluids. However, frequent urination leads to depletion of liquid called dehydration leads to shortage in saliva causing dry mouth and throat. Dehydration increases the osmotic blood pressure and lower blood volume. This makes the kidney to release of rennin angiotensin this stimulates the hypothalamus to signal thirst. Thus, diabetics have frequent thirst and need to drink often.

•Why Lack of Energy & Feeling Tired?

Inadequate insulin secretion or insulin resistance prevents the body to consume the available blood glucose. Additionally, kidney flushes out excess sugar and minerals (such as sodium, chloride, potassium, and bicarbonate) from the body meant for energy that gone unutilized. This lack of glucose absorption, removal of vital minerals and dehydration leads to lack of energy thus diabetic's feel tired.

• Why diabetics are having too much hungry?

In almost 40% of people, the thirst mechanism is so weak that often mistaken for hunger. In addition, when you feel tired, your body signals for energy as hunger. This causes you feel hunger.

• Why diabetics are having blurred vision?

Those who unknowing having diabetes are often happy to note that they do not need glasses anymore to see distance objects (mostly people with myopia or Shortsightedness). This is because, increase or decrease in blood-sugar level makes the eye lens and (or) corneal tissue to swell or shrink respectively, results in varying vision. Others may find their vision turns blur; with respect to how high the blood-sugar level is.

With proper treatment if the blood-sugar level returns to normal, blurred vision (or sometime clear vision) disappears.

• **Why diabetics are having dry and itchy skin?**

Dehydration and inadequate supply of nutrients to the skin makes it, lose its lust and shine. Furthermore, the dehydrated skin result is dull, flaky, rough, and dry skin. Which makes the skin itchy?

• **Why diabetics are losing sense or tingling in their feet?**

Numbness or tingling sensation among healthy individuals when they sit in a position for extended time. This is due to short supply in blood circulation to these areas. Similarly, diabetics with high blood sugar levels are generally short supply of nutrients to the extremities causing numbness or tingling sensation over the feet.

• **Why are diabetics, Sores heals slowly?**

Healing takes longer due to low nutrient supply. In addition, the immune system does not work efficiently in case of high blood sugar, because of the interactions between various hormones and enzymes. Thus, diabetics sore takes longer to heal.

• **Why is diabetic loss or gain weight?**

Some lose weight because of low consumption of the blood glucose due to inadequate insulin. Some with diabetes gain weight because of frequent hunger, continuous dumping of food items and unnecessary fat storage. Thus, diabetics have sudden weight loss or weight gain.

What happens when you have diabetes?³⁴

Diabetes is a condition where the amount of glucose in your blood is too high because the body cannot use it properly. This is because your pancreas doesn't produce any insulin, or not enough insulin, to help glucose enter your body's cells – or the insulin that is produced does not work properly (known as insulin resistance).

- Insulin is the hormone produced by the pancreas that allows glucose to enter the body's cells, where it is used as fuel for energy so we can work, play and generally live our lives. It is vital for life.
- Glucose comes from digesting carbohydrate and is also produced by the liver.
- If you have diabetes, your body cannot make proper use of this

glucose so it builds up in the blood and can't be used as fuel.

What happens in diabetes?⁴

Due to lack or insufficiency of insulin there is high blood glucose in diabetes. Excess glucose in the blood can damage the blood vessels. This leads to several complications like heart disease, kidney damage, nerve damage, eye damage and blindness, impotence and stroke. Diabetes, when not controlled, may raise the propensity for infections. Infections and gangrene of the lower limbs is common in uncontrolled diabetes. This may necessitate an amputation if severe. People with diabetes are also 15 per cent more likely to have an amputation than people without the condition.

What to do when diabetes is diagnosed?⁵

1. Request a referral to a certified diabetes educator and/or a dietitian.
2. Obtain a prescription for a glucometer and testing supplies.
3. Begin to make life style changes.
4. Begin an exercise program.
5. Make healthy food choices.
6. Increase your fiber intake.
7. Decrease portion size.
8. Limit your intake of concentrated sweets.
9. Test your blood sugar at varying times of the day.

Anti-diabetic medication^{25,7}

Type 2 diabetes has been classically thought of as a condition that can be managed initially with diet and exercise. Later, with the progressive failure of insulin secretory capacity, oral agents are generally used to promote insulin secretion (sulfonylureas and repaglinide), to improve insulin action in the liver (metformin), to improve insulin action in muscle and fat (troglitazone), or to delay the absorption of carbohydrates from the meal, allowing the delayed secretion of insulin to catch up with rapid carbohydrate absorption (acarbose or miglitol). Drugs used in diabetes treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, liraglutide and pramlintide, all are administered orally and are thus also called oral hypoglycemic agents or oral antihyperglycemic agents. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors. Diabetes mellitus type 1 is a disease caused by the lack of insulin. Insulin must be used in Type I, which must be

injected. Diabetes mellitus type 2 is a disease of insulin resistance by cells. Treatments include (1) agents that increase the amount of insulin secreted by the pancreas, (2) agents that increase the sensitivity of target organs to insulin, and (3) agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract. Insulin is usually given subcutaneously, either by injections or by an insulin pump. Research of other routes of administration is underway. In acute-care settings, insulin may also be given intravenously. In general, there are three types of insulin, characterized by the rate which they are metabolized by the body. They are rapid acting insulins, intermediate acting insulins and long acting insulins. Examples of rapid acting insulins include:

1. Regular insulin (Humulin R, Novolin R)
2. Insulin lispro (Humalog)
3. Insulin aspart (Novolog)
4. Insulin glulisine (Apidra)
5. Prompt insulin zinc (Semilente, Slightly slower acting)

Examples of intermediate acting insulins include

1. Isophane insulin, neutral protamine Hagedorn (NPH) (Humulin N, Novolin N)
2. Insulin zinc (Lente)

Examples of long acting insulins include

1. Extended insulin zinc insulin (Ultralente)

2. Insulin glargine (Lantus)
3. Insulin detemir (Levemir).

Advantages of Insulin

1. Insulin treatment can also produce a beneficial effect on the insulin secretory capacity of the β -cell, as demonstrated in different studies in newly diagnosed type 2 diabetic subjects naive to pharmacological treatment^{21,22}.
2. Insulin therapy has beneficial effects on β -cell survival and function and on peripheral insulin sensitivity.²³

Adverse effect of Insulin

1. Weight gain - In some patients, weight gain is not the direct effect of insulin. Rather, it depends on the reduction of glycosuria determined by improved metabolic control with consequent reduction of energy waste.²⁴
2. It may increase risk of hypoglycemia. A number of oral glucose lowering drugs is now available such as metformin, sulfonylureas, non-sulfonylureas secretagogues (metiglinides derivatives), alpha glucosidases inhibitors, and the newest agent: thiazolidinediones (TZD).²⁰

Some antidiabetic drugs are⁹

Diabetes Pills	How to take	How they work	Side effects	Of note
Biguanides Metformin (Glucophage) Metformin liquid (Riomet) Metformin extended release (Glucophage XR, Fortamet, Glumetza)	Metformin: Usually taken twice a day with Breakfast and evening meal. Metformin extended release: usually taken once a day in the morning	Decreases amount of glucose released from liver.	Bloating, gas, diarrhea, upset stomach, loss of appetite (usually within the first few weeks of starting). Take with food to minimize symptoms. Metformin is not likely to cause low blood glucose. In rare cases, lactic acidosis may occur in people with abnormal kidney or liver function.	Always tell healthcare providers that it may need to be stopped when you are having a dye study or surgical procedure.
Sulfonylureas Glimperide (Amaryl) Glyburide (Diabeta, Micronase) Glipizide (Glucotrol, Glucotrol XL) Micronized glyburide (Glynase)	Take with a meal once or twice a day.	Stimulates the pancreas to release more insulin, both right after a meal and then over several hours	Low blood glucose, occasional skin rash, irritability, upset stomach	Because these medicines can cause low blood glucose, always carry a source of Carbohydrate with you. Follow your meal plan and activity program. Call your healthcare

				provider if your blood glucose levels are consistently low. If there is an increase in your activity level or reduction in your weight or calorie intake, the dose may need to be lowered.
Meglitinides Repaglinide (Prandin) D-Phenylalanine Derivatives Nateglinide (Starlix)	Both of these Medications should be taken with meals. If you skip a meal, skip the dose.	Stimulate the pancreas to release more insulin right after a meal.	Effects diminish quickly and they must be taken with each meal; may cause low blood glucose.	These work quickly when taken with meals to reduce high blood glucose levels. However, they are less likely than sulfonylureas to cause low blood glucose.
Thiazolidinediones Pioglitazone (TZDs) Pioglitazone (Actos)	Usually taken once a day; take at the same time each day.	Makes the body more sensitive to the effects of insulin.	May cause side effects such as swelling (edema) or fluid retention. Do not cause low blood sugar when used alone. Increased risk of congestive heart failure in those at risk.	Increases the amount of glucose taken up by muscle cells and keeps the liver from Overproducing glucose; may improve blood fat levels. Talk with your healthcare provider if you have the following symptoms: nausea, vomiting, fatigue, loss of appetite, shortness of breath, severe edema or dark urine.
DPP-4 Inhibitors Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Tradjenta)	Take once a day at the same time each day.	Improves insulin level after a meal and lowers the amount of glucose made by your body.	Stomach discomfort, diarrhea, sore throat, stuffy nose, upper respiratory infection. Do not cause low blood glucose.	Can be taken alone or with metformin, a sulfonylurea or Actos. Tell your Healthcare provider if you have any side effects that bother you or that don't go away.
Alpha-glucosidase Inhibitors Acarbose (Precose) Miglitol (Glyset)	Take with first bite of the meal; if not eating, do not take.	Slows the absorption of carbohydrate into your bloodstream after eating	Gas, diarrhea, Upset stomach, abdominal pain	Take with meals, to limit the rise of blood glucose that can occur after meals; these do not cause low blood glucose. Side effects should go away after a few weeks. If not, call your healthcare provider.
Bile Acid Sequestrants Colesevelam (Welchol)	Take once or twice a day with a meal and liquid.	Works with other diabetes Medications to lower blood glucose.	Constipation, nausea, diarrhea, gas, heartburn, headache (may interact with glyburide, levothyroxine and contraceptives)	Primary effect, when used either alone or with statin, is to lower LDL cholesterol; has blood glucose lowering effect when taken in combination with certain diabetes medications. Before taking this medication, tell your healthcare provider if you have high triglycerides (blood fats) or stomach problems. If you take thyroid medication or glyburide, take them 4

				hours before taking Welchol. Tell your healthcare provider if you have side effects that bother you or that don't go away.
Combination Pills Pioglitazone & metformin (Actoplus Met) Glyburide & metformin (Glucovance) Glipizide & metformin (Metaglip) Sitagliptin & metformin (Janumet) Saxagliptin & metformin (kombiglyze) Repaglinide & metformin (Prandimet) Pioglitazone & glimepiride (Duetact)	Check with your provider; Usually taken once a day.	Combines the actions of each pill used in the combination.	Side effects are the same as those of each pill used in the combination. Some combination pills may lead to low blood glucose levels if one of the medications contained in the combination has this effect.	May decrease the number of pills you need to take.

Antidiabetic drugs available in market¹⁰

DRUG NAME (BRAND NAME)	GENERIC NAME	CLASS
Actos	Pioglitazone	Thiazolidinediones
Amaryl	Glimepiride	Sulfonylureas
Avandia	Rosiglitazone	Thiazolidinediones
Bydureon	Exenatide	Incretin mimetics
Byetta	Exenatide	Incretin mimetics
Glucophage	Metformin	Non -sulfonylureas
Glucotrol	Glipizide	Sulfonylureas
Humalog	Insulin lispro	Insulin
Invokana	Canagliflozin	SGLT-2 inhibitors
Januvia	Sitagliptin	Dipeptidyl peptidase 4 inhibitors
Lantus	Insulin glargine	Insulin
Levemir	Insulin detemir	Insulin
Novolog	Insulin aspart	Insulin
Onglyza	Saxagliptin	Dipeptidyl peptidase 4 inhibitors
Prandin	Repaglinide	Meglitinides
Tradjenta	Linagliptin	Dipeptidyl peptidase 4 inhibitors
Victoza	Liraglutide	Incretin mimetics
Welchol	Colesevelam	Bile acid sequestrants.

Banned diabetic drugs^{11, 12}

The ministry of health and family welfare has suspended the manufacture and sale of all three drugs under Section 26A of the Drugs and Cosmetics Act, 1940 with immediate effect, through a notification issued on June 18, informed sources told TOI. While the ministry has been dillydallying on withdrawing analgin and deanxit for years now, despite pressure from a parliamentary panel, the decision on the diabetes drug pioglitazone has taken the industry completely by surprise. The decision to ban pioglitazone and its combinations will hit the Rs 700-crore market for such drugs and adversely impact a clutch of companies including Abbott, Sun Pharma, USV, Lupin, Ranbaxy and Wockhardt. Pioglitazone combination is a bigger market than plain pioglitazone itself which is has posted a strong double-digit growth, with over 30 companies marketing the

drug. The top-selling brands of pioglitazone include Pioz MF G and Pioz (USV), Gemer P (Sun Pharma), Tribet (Abbott), Triptide (Micro Labs) and Gluconorm PG (Lupin). It's believed that pioglitazone can cause heart failure and increases the risk of bladder cancer, analgin has been discarded the world over on grounds of patient safety.

Avandia (rosiglitazone), which is used to treat type 2 diabetes, has already been banned in Europe. It is still available in the United States, but continues to sink in reliability as it is associated with high risk of serious heart ailments including congestive heart failure, heart attack and death compared with a similar drug also used to combat diabetes, pioglitazone (Actos).

Both drugs are thiazolidinediones, first introduced in the late 1990s, that help to control blood sugar levels in patients with type 2 diabetes. On June 6th, 2013, an FDA

advisory panel voted to loosen the restrictions on Avandia (rosiglitazone), which have been in force since 2010. In 2010, the European Medicines Agency suspended the use of rosiglitazone, but in the United States it is still available on a restricted basis. Therefore, a team of researchers in the UK set out to compare the cardiovascular effects of the two drugs among patients with type 2 diabetes. Both drugs attribute to increase heart problem risk. On June 6th, 2013, an FDA advisory panel voted to loosen the restrictions on Avandia (rosiglitazone), which have been in force since 2010. In 2010, the European Medicines Agency suspended the use of rosiglitazone, but in the United States it is still available on a restricted basis. Therefore, a team of researchers in the UK set out to compare the cardiovascular effects of the two drugs among patients with type 2 diabetes. Both drugs attribute to increase heart problem risk.

What is combination therapy?

Monotherapy often fails after a period of treatment, so that multiple drugs are needed to achieve effective glycemic control²⁰. Combination drug therapy is defined as the use of 2 or more pharmacologic agents administered separately or in a fixed-dose combination of 2 or more active ingredients in a single-dosage formulation.¹³ Combination therapy is frequently prescribed by physicians to treat and manage a plethora of medical conditions; however, without thorough monitoring, various problems can arise.¹³ In some cases, patients must try several different combinations of drugs before finding the best therapy to successfully treat a medical condition.¹³ Pharmacists can be instrumental in ensuring that combination drug therapy is used appropriately by screening for potential drug-drug interactions, contraindications, or both, and by making therapeutic recommendations aimed at achieving optimal response without increasing the potential for adverse drug reactions.¹³ Pharmacists also can identify possible cases of polypharmacy, especially among elderly patients and those with multiple medical conditions. Combination drug therapies can offer additive benefits that target multiple pathologic processes.¹³ Combination drug therapy can be used initially or added gradually if the therapeutic response with monotherapy is not as expected. In addition to using 2 or more single agents as a treatment for a medical condition, various fixed dose combination formulations may offer several advantages, such as the convenience of fewer pills a patient is required to take daily

and reduced potential for medication errors. Research has shown that simpler drug regimens may increase the likelihood of patient adherence, and, depending upon the pharmacologic agent, medication costs may also decrease.¹⁴⁻¹⁶ Combined agents also may minimize the adverse effects of each individual agent.¹⁶

Some concerns about using fixed-dose combination drugs include the lack of flexibility in altering the dosing of individual components and the exposure of patients to unnecessary therapy.^{15,17} The FDA's policy on fixed-dose drug combinations states that 2 or more drugs may be combined in a single-dose form when each component makes a contribution to the claimed effects, and the dosage of each component is such that the combination is safe and effective for a significant patient population requiring concurrent therapy as defined in the labeling for the drug.¹⁵

Insulin- Sulfonylurea combination therapy

The major action of sulfonylureas is to promote insulin secretion in response to glucose. Insulin therapy supplements insulin production.²⁵ Thus, the combination of the two merely provides a dual mechanism for increasing insulin levels.²⁵ Nevertheless, substantial clinical trial data suggest that insulin in combination with sulfonylurea at least provides an insulin-sparing effect, reducing the total daily dose of insulin required to achieve a given level of glycemic control, and generally provides for a modest improvement in glycemic control.²⁶ ²⁷Glimepiride is the only sulfonylurea with a Food and Drug Administration (FDA) approved indication for combination therapy with insulin.^{28,29} There is no reason to assume that there are lesser benefits to combination therapy with other sulfonylurea agents, most of which have been studied in combination with insulin.²⁵ Repaglinide is not addressed in this manuscript because no data on its use in combination with insulin are available, though there is no reason to believe that it may not provide benefits similar to those of sulfonylureas in this regard.²⁵

Insulin- Metformin combination therapy²⁵

The combination of metformin and insulin is in fairly widespread use in the U.S. and has recently been approved by the FDA. The rationale for using insulin in combination with metformin is that combining insulin with an agent that is known to sensitize the liver to the action of insulin should be of additive if not synergistic benefit in reducing blood glucose, particularly in the fasting state. Furthermore, it

is attractive to think that the documented effect of metformin to minimize weight gain in the setting of sulfonylurea therapy may likewise provide benefit in minimizing weight gain associated with insulin therapy. Thus, two basic approaches are commonly used and supported by limited clinical trial data. The first is the addition of insulin to patients treated with metformin or with metformin plus sulfonylurea to improve glycemic control. The second is the addition of metformin, with or without sulfonylurea, to insulin treatment with an aim to improve glycemic control, reduce the insulin dose, and/or minimize weight gain. Either approach should be undertaken with gradual titration over a period of several weeks to first normalize fasting glucose and then premeal and postprandial glucose. Care to avoid use of metformin in patients with relative or absolute contraindications (renal, cardiac, hepatic, or pulmonary insufficiency and/ or advanced age or alcoholism) is always a primary concern to avoid the rare but potentially fatal complication of lactic acidosis.

Acarbose- Insulin combination therapy

Combination therapy with insulin and acarbose has been recently approved by the FDA in the U.S.²⁵ The rationale for use of this combination is that acarbose therapy can reduce the postprandial rise in glucose by delaying absorption of dietary carbohydrate and perhaps reduce weight gain like its effect in minimizing weight gain in sulfonylurea-treated patients.³⁰ Acarbose can be added to insulin therapy to improve postprandial glycemic excursions in the patient who consumes a diet rich in carbohydrates.²⁵

Patients treated with acarbose should be counseled to start with a low dose and increase the dose slowly to minimize flatulence as the major adverse event.²⁵

Troglitazone- Insulin combination therapy²⁵

The addition of troglitazone to the treatment regimen of insulin-treated patients with type 2 diabetes has been well studied and is effective in reducing insulin dose and improving glycemic control. This combination is approved by the FDA and was the initial indication for which troglitazone was approved in 1997. The rationale is to combine an insulin-sensitizing agent whose predominant effect is an improvement in the action of insulin in peripheral tissues, namely muscle and fat, with exogenous (e.g., peripheral) insulin administration. The benefit of this combination has been well established through twin studies that attempted to isolate the insulin-sparing effect of troglitazone from the effect of

troglitazone to improve glycemic control in subjects with type 2 diabetes treated with insulin.

Metformin- Repaglinide combination therapy³¹

The Food and Drug Administration (FDA) approved PrandiMet, the first and only fixed-dose combination that comprises a fast-acting secretagogue repaglinide (Prandin) and insulin sensitizer, metformin, for patients unable to achieve glycemic control using the single therapy of meglitinide or metformin. Repaglinide reduces postprandial glucose (PPG) by stimulating the release of insulin from the pancreas after a meal. Metformin decreases hepatic glucose production, increases peripheral glucose uptake, and improves insulin sensitivity.

Tips to remember PrandiMet³¹

1. Take PrandiMet within 15 minutes prior to meals.
2. If patients skip a meal, they should skip the PrandiMet dose for that meal.
3. PrandiMet is contraindicated in patients receiving gemfibrozil or itraconazole.
4. Counsel patients to avoid alcohol since it increases the effect of metformin on lactate metabolism.
5. PrandiMet is available in two tablet strengths (repaglinide/ metformin): 1 mg/500 mg and 2 mg/500 mg.
6. Other contraindications include using this medication in patients with metabolic acidosis and diabetic ketoacidosis. PrandiMet should also be avoided in patients with hepatic impairment.

Combination therapy with Dapagliflozin³²

Dapagliflozin (Forxiga, Bristol-Myers Squibb and AstraZeneca) is a sodium-glucose cotransporter-2 (SGLT-2) inhibitor that blocks the reabsorption of glucose in the kidneys and promotes excretion of excess glucose in the urine. It has a UK marketing authorisation 'in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

- Monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.
- Add-on combination therapy with other glucose-lowering agents including insulin, when these, together with diet

and exercise, do not provide adequate glycaemic control.

Adverse reactions for dapagliflozin: hypoglycaemia (when used with a sulfonylurea or insulin), urinary tract and genital infection, back pain, dysuria, polyuria, dyslipidaemia and elevated haematocrit. Dapagliflozin is also not recommended for use in combination with pioglitazone.

Metformin- Sitagliptin combination therapy³³

Sitagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4). This enzyme rapidly metabolizes the endogenous incretins, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). In response to the presence of food, GLP-1 is released from the endocrine L cells of the lower small intestine/ colon and GIP from K cells in the upper small intestine. Both hormones increase insulin secretion when plasma glucose concentrations are above the normal fasting range. They have an additive effect, but GLP-1 inhibits gastrointestinal motility and gastric emptying, and reduces appetite and food intake to a greater extent than GIP, and also attenuates glucagon secretion. DPP-4 inhibition increases plasma concentrations of GLP-1 and GIP, which are reduced in patients with type 2 diabetes, and therefore has a variety of beneficial effects on glycaemia. Metformin acts by reducing hepatic glucose production, mainly due to inhibition of gluconeogenesis. It also increases non-oxidative skeletal muscle glucose disposal and, because of consequently less 'glucotoxicity', it can improve residual pancreatic beta-cell function. At a molecular level, metformin increases insulin-mediated insulin receptor tyrosine kinase activity, which in turn augments a range of insulin signals. It also increases the activity of glucose transporters and indirectly activates adenosine mono-phosphate-activated protein kinase. Established adverse events associated with metformin include diarrhoea, nausea, vomiting, flatulence, abdominal discomfort, indigestion, asthenia and headache. Nevertheless, up to 5% of patients in trials of sitagliptin monotherapy experienced nasopharyngitis. Rare hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, cutaneous vasculitis and Stevens-Johnson syndrome, have also been reported from postmarketing surveillance in patients

treated with sitagliptin. Sitagliptin and metformin combination therapy is contraindicated in patients:

- with renal disease or renal dysfunction, usually a serum creatinine level of 133 $\mu\text{mol/L}$ or above in males or 124 $\mu\text{mol/L}$ or above in females, or an estimated creatinine clearance of less than 60 mL/min/1.73 m². This is because sitagliptin is primarily excreted unchanged in the urine through active tubular secretion, and metformin can also accumulate in patients with renal failure. Sitagliptin and metformin combination therapy should also be temporarily discontinued in patients undergoing radiological studies involving intravascular administration of iodinated contrast materials that may impair renal function.
- with known hypersensitivity to sitagliptin or metformin.
- with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. This relates to the reported association between metformin and lactic acidosis, the occurrence of which remains rare.
- who are pregnant or lactating.

Usefulness of combination in diabetic Conditions^{18,19}

Combination drug therapy is often used to treat diabetes. Some of the advantages of using combination drug therapy in diabetes include the following:

- Better glycemic control with 2 drugs that work at different sites
- Fewer side effects with lower doses of 2 drugs than a large dose of 1 drug
- When combined in the same pill or capsule, the likelihood of patient adherence to therapy may increase and the cost may be lower, depending on the agent.

Patients with type 2 diabetes may also require other medications to treat or prevent disease-associated complications. Aspirin and statins are often used for cardioprotection, and ACEIs/ARBs are used for renal protection.

Combination approved by FDA²⁰

COMPOUND	APPROVED FDA ASSOCIATION
METFORMIN	Monotherapy
	Sulphonylurea
	Non- sulphonylurea
	Alpha- glucosidase inhibitor
	Thiazolidinediones
	Insulin
Sulphonylurea	Monotherapy
	Metformin
	Thiazolidinediones
	Alpha- glucosidase inhibitor.

Antidiabetic combinations¹⁰

A drug may be classified by the chemical type of the active ingredient or by the way it is used to treat a particular condition. Each drug can be classified into one or more drug classes.

Antidiabetic combinations are medicines with two or more classes of antidiabetic agents (with different mechanisms of action) in one pill or dose. Just having one pill may improve compliance and better glycemic control.

DRUG NAME (BRAND NAME)	GENERIC NAME
ActoPlus Met XR	Metformin / Pioglitazone
Avandamet	Metformin / Rosiglitazone
Avandaryl	Glimepiride / Rosiglitazone
Duetact	Glimepiride / Pioglitazone
Glucovance	Glyburide / Metformin
Janumet	Metformin / Sitagliptin
Jentadueto	Linagliptin / Metformin
Juvisync	Simvastatin / Sitagliptin
Kazano	Alogliptin / Metformin
Kombiglyze XR	Metformin / Saxagliptin
Metaglip	Glipizide / Metformin
Oseni	Alogliptin / Pioglitazone
PrandiMet	Metformin /Repaglinide . ¹⁰

CONCLUSION

Diabetes has emerged as a major healthcare problem in India which is associated with β cell failure. According to Diabetes Atlas published by the International Diabetes Federation (IDF), there were an estimated 40 million persons with diabetes in India in 2007 and this number is predicted to rise to almost 70 million people by 2025. Followed by China (43.2 million) and the United States (26.8 million), reveal new figures released by the International Diabetes Federation (IDF). Combination drug therapy is often used to treat diabetes. Antidiabetic combinations are medicines with two or more classes of antidiabetic agents (with different mechanisms of action) in one pill or dose. Just having one pill may improve compliance and better glycemic control. Advantages of combination therapy are better glycemic control with 2 drugs that work at different sites, fewer side effects with lower doses of 2 drugs than a large dose of 1 drug, when combined in the same pill or capsule, the likelihood of patient adherence to therapy may increase and the cost may be lower, depending on the agent.

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