



## Review Article

### A COMPARATIVE STUDY OF DRUG INTERACTION AND SIDE-EFFECT OF DRUG FOR TREATMENT OF DIABETES MELLITUS: A REVIEW

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#### ABSTRACT

The objective of this review paper is to examine diabetes and via the modifying drugs treatment how to improve the patient condition and related risks. The review mentions the different types of comparative drugs which are useful for diagnosis or prevention of diabetes. Treatment modification can play a major role in the decreasing the diabetic patients. In India, a concerning 1-5% by population affected by diabetes or related difficulty. So there is required to use medications to cure the disease. If a patient suffers from diabetes used anti-diabetic drugs. These drugs are recommended for lowering the blood glucose levels. Metformin, Acarbose, thiazolidinedione etc. Most of the drugs are administered via orally so that called oral hypoglycemic or oral antihyperglycemic agents. Present days for treatment of diabetes available, different classes of anti-diabetic drugs and their choice depending on the patient diabetic type or the condition, age as well as other factors. Type 1 diabetes mainly caused by deficiency of insulin secretion the body. Researcher around the world focused on oral hypoglycemic agents and presents various types of comparative study to control the diabetes mellitus. The present review summarizes the comparative study of anti-diabetic drugs for the treatment of diabetes. This review article has shown a comparative study of drugs which are metformin more popular drug treatment of diabetes and they have the less side effect or higher efficacy, mention in the recently published articles.

**Keywords:** Diabetes Mellitus, Blood glucose level, oral antihyperglycemic agents, Sulphonylurea, Metformin

#### INTRODUCTION

Recently, Diabetes most popular disease which is characterized by a group of metabolic disorder high blood glucose level in the blood (hyperglycemia) <sup>1</sup>. Diabetes is not a single disorder it is a heterogeneous disorder affecting the irregular insulin secretions and insulin actions. <sup>2</sup>More than 230 million people worldwide are affected; diabetes mellitus. Diabetes is caused due to decrease the level of insulin or resistance to insulin or both<sup>1</sup>.

Prolong beta-cell failure or damage causes the diabetes mellitus, a diabetic patient has lost over 80% of their beta cell function. So, rapidly patient treatment with anti-hyperglycaemic drugs they give positive effects<sup>3,4</sup>. Metformin is recommended as a first line drug in the treatment of diabetic patients, because of metformin less expensive, does not cause weight gain and have a beneficial effect on the cardiovascular system. Some other drugs have also recommended as an alternative drugs sulphonylurea, thiazolidinedione, and dipeptidyl peptidase4 (DPP-4) inhibitors. The major problems are diabetic neuropathy and nephropathies, foot ulcer and limb amputation, a peripheral vascular disease affecting 30% of those aged 40. Polyuria, polydipsia, weight loss, blurred vision and sometimes with polyphagia are included symptoms of diabetes<sup>5</sup>.

Diabetes is a chronic disease that requires continues treatment for prevention and lifestyle modification plays a major role for preventing acute Complication<sup>6</sup>. If blood glucose level cannot be

controlled by a single agent, use another oral agent or insulin. The effective oral combination is sulfonylurea plus metformin<sup>7</sup>. This combination full dosage can reduce HbA1C by 2%. The present study objective is comparing the efficacy of oral hypoglycemic agents<sup>8</sup>. Although different reports of the consequence of the problem, the documentation suggested that the rate of diabetes higher, which is essential to be knock down the price with adequately.

#### TREATMENT OF DIABETES MELLITUS

##### Medication

##### Biguanides [Metformin]

Metformin has been available since the 1950s and its origin can be Galega officinalis which have traditionally been used the treatment of diabetes. Metformin has a variety of medicinal action. Metformin modes of action have not clearly established. However, it is thought that insulin sensitivity or improved and mediated by the modification of post-receptor signaling in the insulin pathway. A protein, adenosine 5-monophosphate protein kinase, has been shown a possible target of metformin. This type of drug mainly attributed to its hepatic effects. Metformin action based on hepatic sensitivity to insulin is frequently increased, thereby decreasing or reducing the gluconeogenesis as well as glycogenolysis, which helps contributes the post-prandial plasma glucose lowering effects<sup>8,9</sup>. Skeletal muscle and adipocytes are

responsible for regulation of insulin-sensitive GLUT-4 and GLUT-1 transporters to the cell membrane thereby increasing the level of glucose uptake. Glucose metabolism also increases the splanchnic bed and further suppression of fatty acid oxidation as well as triglyceride lowering due to metabolism effects. Metformin rapidly absorbed and eliminated through the urine via tubular secretion. This drug not binds to plasma proteins and is not metabolized.

#### Side-effects

Metformin may cause a serious condition called lactic acidosis with the following symptoms: severe drowsiness, muscle pain, tiredness, Dizziness, chills, blue/cold skin, slow/irregular heartbeat, fast/difficult breathing, stomach pain with diarrhoea, vomiting or nausea. This drug is portal venous system due to a reduction in the activity of pyruvate dehydrogenase enzyme, thereby shifting the metabolism. Metformin most frequently affects the abdominal discomfort and diarrhoea and the drug also may cause vitaminB12 deficiency due to decreased GIT absorption take place<sup>10</sup>.

#### Drug interaction

Drugs affecting Metformin, Iodinated in the stomach or duodenum can lead to acute renal failure and metformin, Alcohol cause to be potent; make powerful lactate metabolism<sup>11</sup>.

#### Thiazolidinedione's (Pioglitazone, Rosiglitazone)

Peroxisome proliferator-activated receptor PPAR- $\gamma$  is agonists with anticipation. The overall effect of this drugs results from stimulation of a nuclear PPAR- $\gamma$  that regulate the transcription of genes by for increasing the insulin sensitivity. PPAR- $\gamma$  receptor binds to the thiazolidinedione's or mediates their faction that expressed predominantly in adipocytes.

Glitazones a newer class drug which is improving metabolic control in the diabetic patient through the improvement of insulin sensitivity. Their mechanism of action involves activation of the peroxisome proliferator-activated receptor (PPAR gamma). Thiazolidinedione's induced or activation of PPAR gamma, a nuclear receptor that alters the transcription of several genes those are responsible for lipid and glucose metabolism and also play a role energy balance, including code the lipoprotein lipase, transport the fatty acid protein, fatty acyl-CoA synthase, adipocyte fatty acid, glucokinase and GLUT4 glucose transporter. Thiazolidinediones reduce insulin resistance in muscle, liver and adipose tissue. The effect of TZDs on insulin resistance in liver and muscle is promoted via signaling of endocrine from adipocytes. They have potential signaling factors include free fatty acid or adipocyte-derived tumor necrosis TNF-alpha, which is expressed in obesity and insulin resistance<sup>11</sup>.

#### Side Effect

TZDs have some commonly experienced side effects fluid retention and weight gain (around 1- 4 kg over 6-12 months) is a major effect, worsening of cardiac failure with edema, anemia due to haemodilution and liver toxicity<sup>12</sup>.

#### Drug Interaction

Thiazolidinedione drugs pioglitazone and rosiglitazone can both take without regard to meals. Rosiglitazone is a substrate for CYP2C8 and pioglitazone is a substrate for CYP2C8 (39%) and rosiglitazone lesser extent CYP2C9 pathway, and CYP3A4 (17%), have also several other pathways CYP450.Both are

metabolism in vivo can be inducers of CYP2C8 or affected by the inhibitor, but no significant reported to drug-drug interaction and neither drug have eliminated through the drug-drug interaction<sup>13</sup>.

#### Sulfonylureas (glibenclamide, gliclazide, glipizide, glimepiride)

Sulfonylureas are used for treating non – insulin dependent diabetes mellitus. Sulfonylureas provoke actively release of insulin from the pancreatic  $\beta$ -cell. The drug gliclazide bind to the

$\beta$  – cell sulfonylureas receptor. The drug, a primary mechanism of action decreases the conductance or block ATP- sensitive potassium channels. The binding result decreases the potassium efflux or increases the Ca<sup>2+</sup> influx leads to degranulation of  $\beta$ -cells. This calcium channel activation of calmodulin, which leads to exocytosis of insulin secretory granules. In recent a study has expressed the  $\beta$ -cell ATP sensitive K-channel have two phases- 1 phase is pore-forming subunit and 2<sup>nd</sup> phase is drug binding<sup>14</sup>.

#### Side Effect

Sulphonylurea has some side effects including Skin reaction, acute porphyria, weight gain and rarely hypernatremia, flatulence, constipation. The drug glimepiride also induced acute cholestasis hepatitis.

#### Drug Interaction

Sulfonylureas may occur with drug-drug interaction. Sulfonylureas the first generation may cause a facial flushing reaction due to ingested alcohol with chlorpropamide. Similarly, they caused disulfiram, which blocks aldehyde dehydrogenase, and raises the level of acetaldehyde that can result in flushing and vomiting or nausea at higher level<sup>15</sup>.

#### Alpha glucosidase inhibitor (Acarbose)

Acarbose was the first glycosidase inhibitor drug. The alpha glycosidase inhibitor inhibits the activity of the glycosidase enzymes which are present in the border of enterocytes in the intestinal villi. It is complex oligosaccharide cleavages which reversibly prevent or decrease in intestinal carbohydrate absorption.  $\alpha$ -glycosidase inhibitors reduce postprandial insulin concentrations through that increase the postprandial glucose levels. It is broken down by intestinal amylases and bacteria.

#### Side effects

Acarbose includes flatulence, diarrhoea, abdominal discomfort, and hypoglycemia can also occur only if conjunction with a sulphonylurea or insulin<sup>17</sup>. Short bowel syndrome, Crohn's disease or Ulcerative colitis is certain side effects.

#### Drug Interaction

Acarbose is extensively metabolized, neither has significant metabolism interaction. Several data results have documented a reduce the absorption of digoxin and increase in absorption of warfarin.  $\alpha$ -glucosidase inhibitor are related to the drug-disease interaction induces the gastrointestinal effects, which could cause the patient several types of gastrointestinal disease<sup>18</sup>.

#### CONCLUSION

I have extensively reviewed subcategories of drugs used for treating diabetes. Day by day diabetes increases the number of patients. It is essential that information about drugs through

available treatment modalities awareness programs, clinics, and hospitals waiting for areas. In several studies indicate use of metformin is more beneficial in insulin resistant. According to my view metformin more effective in comparison to other drugs they have high efficacy or less side effects.

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