

# NOVEL DRUGS FOR THE TREATMENT OF DIABETES MELLITUS

## Abstract

Diabetes mellitus is a chronic metabolic illness in which the metabolism of carbohydrates, lipids and proteins is disturbed, resulting in hyperglycemia. The pharmacotherapy of diabetes depends on the type of diabetes mellitus and ranges from insulin preparations, insulin secretagogues, insulin sensitizers to newer class of incretin mimetics.

**KeyWords:** hyperglycemia, insulin secretagogues, incretin mimetics.

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## I. INTRODUCTION

Diabetes mellitus is a chronic metabolic illness due to absence or relative deficiency of insulin. The uptake and metabolism of glucose in the peripheral tissues mainly skeletal muscles and adipose tissue is primarily regulated by insulin. Deficiency of insulin leads to disturbance in the metabolism of carbohydrates, lipids and proteins, resulting in hyperglycemia. Long term exposure of tissues to consistently raised levels of glucose leads to a number of microvascular and macrovascular complications with damage to the kidneys, eyes, nerves, ulceration and can even lead to gangrene of the extremities.[1-3] The severity and duration of the hyperglycemic state is indicated by glycosylated hemoglobin.[4]

**Diabetes Mellitus has been classified into Four Categories Namely:**

- Type 1 or Insulin dependent diabetes mellitus- IDDM
- Type 2 or Non insulin dependent diabetes mellitus- NIDDM
- Type 3 or Other
- Type 4 or Gestational diabetes mellitus

## II. TYPE 1 DIABETES MELLITUS

Type 1 Diabetes Mellitus is an autoimmune disorder in which autoantibodies are formed against the beta cells of the pancreas which produce insulin. These autoantibodies destroy the beta cells leading to loss of insulin production. Hence, there is little or no insulin in the body. Therefore, for treating IDDM, along with dietary and lifestyle modifications, exogenous insulin has to be supplied regularly with strict monitoring of blood glucose levels. [5] There are various types of insulin preparations available, differing in their onset of action, duration of action and the source from which they are derived and have been categorised accordingly. These preparations are mentioned below:

- **Ultra Short Acting Insulin** :insulin lispro, insulin aspart, insulin glulisine
- **Short Acting Insulin** : regular insulin
- **Intermediate Acting And Long Acting Insulin** : NPH ( neutral protamine Hagedorn, or isophane) insulin, insulin glargine, insulin detemir

All these types of Insulins are given subcutaneously ( regular insulin can be given intravenously also ) and have to be given frequently ( dose scheduled with meal times ).[6] It is very crucial to calculate and administer the appropriate dose of insulin at all times. Improper dosage of insulin can lead to hypoglycemic episodes, therefore, there is need for round the clock regulation of blood sugar levels, in a convenient and cost effective manner. For this, new insulin delivery devices can be tried.

**These are**

- **Portable pen injectors** with prefilled insulin cartridges and replaceable needles.
- **Continuous subcutaneous insulin infusion pumps**- These pumps are based on self monitoring of blood glucose levels and are quite user friendly. They help to deliver basal and bolus doses of insulin as per the need of the individual.
- **Subcutaneous Pellet Implants**.

Oral and inhalational insulin preparations are also being developed.

1. **Oral Insulin:** is being tried which is liposomal encapsulated and is not degraded in the stomach but it is quite expensive . [7]
2. **Inhaled Insulin:** is recombinant regular human insulin which can be given in both type 1 and type 2 diabetes. In type 1 diabetes mellitus , it is used with long acting insulin.[8]. It is available in powder form and when inhaled, it reaches the lungs. It acts within 10 to 15 minutes and the action lasts for about 3 hours. It is given just before meals to control prandial hyperglycemia. [9] Inhaled insulin is contraindicated in lung disease. The major adverse effects are decreased blood sugar, cough and sore throat.
3. **Teplizumab:** is a new drug which is useful for the treatment of type one diabetes mellitus (IDDM). It is a highly selective, a CD3-directed monoclonal antibody. The main aim of giving Teplizumab is to delay the onset of Stage 3 type 1 diabetes in individuals suffering from Stage 2 Type 1 Diabetes and above 8 years of age. In IDDM, immune cells act on the beta cells of the pancreas which are responsible for secretion of insulin. The immune cells damage and inactivate the beta cells, causing depletion of insulin in the body. Teplizumab counters the effect of these immune cells and hence mitigates the rate of destruction of pancreatic beta cells. [10-11] The decline in the rate of insulin production is hampered .Subsequently, there is a delay in the onset of stage 3 type 1 diabetes. Regular monitoring of complete blood counts and liver enzymes is required to be done before starting and during treatment with Teplizumab. Teplizumab is administered by IV infusion once daily for 14 days (slow infusion over 30 minutes). Care should be taken so as not to administer two doses of the drug on the same day. It is available as Injection- 2mg/2ml (1mg/1ml) as a single dose vial.

There are several contraindications to the use of Teplizumab like pregnancy, lactation, serious infection, severe decrease in lymphocyte count and severe hypersensitivity reactions. The adverse effects seen are decreased WBC count, rash and headache. There is risk of serious infections and hypersensitivity reactions too. Cytokine release syndrome (CRS) is an important dangerous adverse effect of Teplizumab. CRS may present as pyrexia, nausea, tiredness, headache and arthralgias. The liver enzymes are also raised. Administration of antipyretics, antihistamines and antiemetics before starting the treatment mitigates these symptoms. Throughout the therapy, lymphocyte count and liver enzymes must be monitored regularly.

### III. TYPE 2 DIABETES MELLITUS

In this type diabetes, there is insulin resistance i.e.decrease in the sensitivity of target tissues to insulin. Here antidiabetic drugs are given to reduce the levels of blood glucose level .These drugs act by different mechanisms-

1. By increasing the secretion of insulin, hence, also called **insulin secretagogues** like **Sulfonylureas** ( Glipizide, Glyburide, Glimpride) and **Meglitinides** ( Repaglinide, Nateglinide)- These act on the sulfonylurea receptors present on the beta cells of pancreas and stimulate the release of insulin . ( K<sup>+</sup> ATP channel blockers )

2. By increasing peripheral utilization of glucose like **Biguanides** (Metformin) and **Thiazolidinediones** ( Pioglitazone, Rosiglitazone) - **insulin sensitisers**- They act by increasing the sensitivity of target tissues to insulin and also decrease gluconeogenesis. Biguanides act as AMP K( AMP activated protein kinase ) activators while Thiazolidinediones act as PPAR (peroxisome proliferator-activated receptor) gamma activators.
3. By decreasing the absorption of glucose from the gut- like **alpha glucosidase inhibitors** ( Acarbose, Voglibose, Miglitol ) – These drugs prevent the intestinal absorption of carbohydrates along with increased hydrolysis of disaccharides. [12-15]
4. **Incretin Mimetics** : Incretins like Glucagon like peptides (GLP-1) are chemical mediators released from the special L cells in the ileum and colon in response to oral glucose administration . GLP-1 acts on the pancreas within 2-4 minutes, enhances insulin secretion but can't be given orally because it is rapidly destroyed by DPP4 enzyme ( dipeptidyl peptidase 4) .In type 2 diabetes, production of incretins decreases and their rate of inactivation is increased so they are unable to cause insulin secretion in response to elevated blood glucose levels, leading to hyperglycemia.

Therefore, in order to circumvent this rapid degradation of incretins , drugs which either act as artificial long-acting GLP-1 analogues or which prevent the DPP4 enzyme from acting on its substrate, are needed. These are **GLP-1 receptor agonists** and **DPP4 inhibitors** respectively.

- **They regulate blood glucose levels by the following mechanisms:**

- Enhance secretion of insulin
- Decrease glucagon secretion
- Delay gastric emptying ( food remains in the stomach for a longer time ) and
- Decrease appetite (allay hunger , imparting a feeling of satiety) .[16]

Both GLP1 receptor agonists and DPP4 inhibitors tend to improve the functioning of beta cells , and have been found to increase their lifespan thus posing a potential risk of cancer due to reduced apoptosis.

- **GLP-1 Receptor Agonists:** Exenatide is the first synthetic GLP -1 analogue developed.
  - Others are-
  - Dulaglutide
  - Exenatide
  - Liraglutide
  - Lixisenatide
  - Semaglutide
  - Tirzepatide

All of these drugs are given as injections except Semaglutide , which is an oral formulation.

The adverse effects of GLP-1 receptor agonists are related to GIT like nausea, diarrhoea and constipation. These can be minimized by starting with low dose and increasing the dosage gradually.

Besides controlling blood glucose levels, Semaglutide and Liraglutide also lower the risk of serious cardiovascular problems, such as heart attack and stroke. Hence they are increasingly being used as antidiabetic agents in obese individuals.

- **Tirzepatide** – is a novel drug useful in type 2 diabetes mellitus, when in spite of dietary restriction and exercise, the recommended blood sugar levels are not achieved.[17-19] Tirzepatide activates GLP-1 receptors. In addition to this, it also acts as an agonist on glucose-dependent insulinotropic polypeptide (GIP) receptors. These two hormones play an important role in maintaining blood glucose levels. Nausea, vomiting, diarrhea, decreased appetite, constipation, abdominal discomfort and abdominal pain are some of the adverse effects seen with Tirzepatide.
- **DPP4 inhibitors-** dipeptidyl peptidase 4 inhibitors:
  - Sitagliptin
  - Vildagliptin
  - Sitagliptin
  - Saxagliptin
  - Linagliptin
  - Alogliptin
  - Teneligliptin

These drugs are orally active selective inhibitors of DPP4 and potentiate the action of GLP-1 by inhibiting its degradation by DPP4. Consequently they enhance insulin release in response to oral administration of glucose, inhibit the release of counterregulatory hormone glucagon, slow down gastric emptying and suppress appetite. They have longer plasma half life, are used along with sulfonylureas or metformin in resistant type 2 DM. Side effects- Nasopharyngitis, GIT upset, diarrhoea.

- **Incretin mimetics** can lead to loss of as much as 20% body weight. They also improve blood pressure and cholesterol levels. Therefore, there is significant rise in their use.

Another promising group of drugs for treatment of type 2 diabetes mellitus are the sodium-glucose co-transporter-2 inhibitors **SGLT-2 Inhibitors**. [20] SGLT 2 is present in the proximal tubule where it absorbs glucose. SGLT-2 inhibitors decrease the reabsorption of glucose from the renal tubules, so there is an increased elimination of blood glucose into the urine. These drugs are-

- Canagliflozin
- Dapagliflozin
- Empagliflozin
- Ertugliflozin.

Besides regulating blood sugar levels, these drugs help to reduce blood pressure ( decrease sodium absorption too ) and promote weight loss. Hence they control associated hypertension also.

**Side Effects:** genitourinary infections, constipation, flu-like symptoms, dehydration , low blood pressure that can result in dizziness and fainting , impaired kidney function.

Hypoglycemia can occur when these are used in combination with insulin or insulin secretagogues.

They have been found to improve cardiovascular functioning in both diabetic and non-diabetic individuals. Therefore SGLT-2 inhibitors are gaining use to lower glucose levels in type 2 diabetics who are at high risk of cardiovascular events.

SGLT2 inhibitors are gaining popularity in combination with Metformin and DPP4 inhibitors these days.

#### IV. MISCELLANEOUS DRUGS

##### 1. Amylin Analogs

- **Pramlintide:** which decreases the secretion of glucagon, delays gastric emptying and decreases appetite . It is given by the subcutaneous route.
- **Cagrilintide:** new long acting amylin analogue. It shows overlapping effects with GLP-1 agonists like Semaglutide.

Pramlintide is a shorter acting drug given before meals whereas Cagrilintide can be given once weekly dose with Semaglutide to control blood glucose levels.

2. **Selective Peroxisome Proliferator-Activated Receptor (PPAR) Modulators- Glitazars- Saroglitazar:** are dual peroxisome proliferator activated receptor (PPAR ) agonists. i.e. have affinity for both PPAR alpha ( reduces blood lipids ) similar to fibrates and PPAR gamma ( reduces blood glucose ) similar to glitazones. It decreases levels of triglycerides, LDL cholesterol, and blood glucose. Hence useful in diabetic dyslipidemia.[21]
3. **Ranolazine:** an antianginal drug , decreases glycosylated hemoglobin in experimental models.
4. **Epalrestat:** In hyperglycemia,, excess glucose gets converted to sorbitol by the help of enzyme aldose reductase. This sorbitol then gets deposited in various tissues especially nerves causing diabetic neuropathy. Epalrestat is an aldose reductase inhibitor . It delays accumulation of sorbitol. and is useful in diabetic neuropathy. Side effects are nausea , vomiting and liver dysfunction.

5. **Sevelamer:** It is primarily a phosphate binder with **Bile acid sequestrant** properties. It also decreases the levels of HBA1C, cholesterol and triglycerides. It increases the delivery of bile acids to the distal colon thereby promoting the release of GLP-1
6. **Sotagliflozin:** It is a dual SGLT1 /2 inhibitor. SGLT 1 is present in the gut, SGLT1 and 2 are present in the kidneys. Therefore, Sotagliflozin regulates blood glucose levels by inhibiting the intestinal as well as renal absorption of glucose.
7. **Retatrutide:** This drug targets three hormones – GLP-1 and GIP similar to Tirzepatide and in addition glucagon.
8. **Glimins: Imeglimin-** improve overall functioning of the mitochondria present in the pancreas, liver and muscles for better control of blood glucose levels.
9. **Bromocriptine:** is a drug used for the treatment of Parkinsonism, also regulates blood glucose levels.

## V. NOVEL DRUG TARGETS

Various Receptors, enzymes, transporters and ion channels can be studied for their potential to decrease blood glucose levels by enhancing release of insulin or by enhancing the responsiveness of target tissues to insulin.

### 1. Receptors

- GPR119, Glucose-dependent insulinotropic receptor (G-Protein coupled receptor 119)- is expressed in several endocrine cells and stimulates insulin and incretin secretion.
- Glucagon receptor antagonists.
- Leptin analogues
- Adiponectin receptor agonists
- Analogues of fibroblast growth factor-21
- GIPR, Gastric Inhibitory Polypeptide Receptor
- AMPK, 5'-AMP-activated protein kinase.
- Thyroid hormone receptors (THR) are present in significant numbers in the liver, skeletal muscles, and kidneys. In experimental models, THRs have demonstrated to increase insulin sensitivity, and lower glucose levels.

## VI. ENZYMES

- DGAT ( diacylglycerol acyltransferase ) inhibitors increase insulin sensitivity and protect beta cells. [22]
- Bradykinin type 2 receptors(BK2R)- increase glucose uptake, enhance insulin sensitivity and reverse insulin resistance.
- Fructose 1-6 biphosphatase 1 enzyme inhibitor (this enzyme causes gluconeogenesis).
- Methionine aminopeptidase
- Angioprotein related protein 3 inhibitors .increase insulin sensitivity

Overall, if we compare the different antidiabetic agents, in terms of economic burden the Sulfonylureas, Meglitinides and Thiazolidinediones (TZDs) are most cost effective . DPP4 inhibitors and SGLT2 inhibitors are highly effective but are most expensive of all. In terms of adverse effect profile , hypoglycaemia and weight gain are the major adverse effects seen with Sulfonylureas and Meglitinides whereas Thiazolidinediones cause weight gain, oedema, heart failure and bone fractures.

In India, metformin is the most preferred first-line drug followed by DPP4 inhibitors . In recent times, SGLT2 inhibitors are also being increasingly used as add on third- or fourth-line antidiabetic drugs .

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