**Novel Drugs for the treatment of**

**Diabetes mellitus**

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**Abstract**

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

**Key words-** hyperglycemia, insulin secretagogoues, incretin mimetics.

**Introduction**

Diabetes mellitus is a chronic metabolic illness due to absolute or relative deficiency of insulin. Insulin is the major hormone that regulates the uptake and metabolism of glucose in the peripheral tissues mainly skeletal muscles and adipose tissue. Deficiency of insulin leads to deranged metabolism of carbohydrates, lipids and proteins , most important being hyperglycemia. Prolonged exposure of tissues to elevated levels of glucose leads to several complications including premature atherosclerosis, nephropathy, retinopathy, neuropathy, ulceration and 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-

1. Type 1 or Insulin dependent diabetes mellitus
2. Type 2 or Non insulin dependent diabetes mellitus
3. Type 3 or Other
4. Type 4 or Gestational diabetes mellitus

**Type 1 diabetes mellitus** is an autoimmune disorder in which autoantibodies are formed against the insulin producing beta cells of the pancreas. As a result beta cells get destroyed , and there is little or no insulin in the body. Hence the only treatment is administration of exogenous insulin regularly with monitoring of blood glucose levels along with dietary and lifestyle modifications. [5] There are various types of insulin preparations available. They vary in their onset of action, duration of action and the source from which they are derived . These preparations are mentioned below-

1. Ultra short acting insulin - insulin lispro, insulin aspart, insulin glulisine
2. Short acting insulin - regular insulin
3. 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-

1. **Portable pen injectors** with prefilled insulin cartridges and replaceable needles.
2. **Continuous subcutaneous insulin infusion pumps** which have a user- programmable pump that delivers individualized basal and bolus doses of insulin base on blood glucose self monitoring results.
3. **Subcutaneous pellet implants** .

Oral and inhalational insulin preparations are also being developed.

**Oral insulin** is being tried which is liposomal encapsulated and is not degraded in the stomach but it is quite expensive **.** [7]

**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 inhaled as a powder and is delivered to 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 ontraindicated in lung disease. The major adverse effects are decreased blood sugar, cough and sore throat. **Teplizumab-** is a new drug which is useful for the treatment of type one diabetes mellitus. It is a highly selective, a CD3-directed monoclonal antibody, for delaying the onset of Stage 3 type 1 diabetes in adults and paediatric patients aged 8 years and older with Stage 2 Type 1 Diabetes. It binds to the immune cells that destroy the insulin producing pancreatic beta cells and inactivates them , hence the decline in the rate of insulin production is decreased and subsequently delay in the onset of stage 3 type 1 diabetes. Teplizumab slows down the rate of destruction of pancreatic beta cells.[10-11] Before starting treatment , complete blood counts and liver enzymes should be obtained. Teplizumab is administered by IV infusion once daily for 14 days ( slow infusion over 30 minutes). Two doses of the drug should not be administered on the same day. It is available as Injection- 2mg/2ml ( 1mg/1ml) as a single dose vial.

Teplizumab is contraindicated in pregnancy , lactation , acute serious infection or chronic infection , severe lymphopenia and in case of severe hypersensitivity reactions. The adverse effects seen are decreased WBC count, rash and headache. There is risk of serious infections, hypersensitivity reactions and Cytokine release syndrome (CRS). CRS may present as fever, nausea, fatigue, headache, arthralgia, raised liver enzymes. Premedication with antipyretics, antihistamines and antiemetics mitigates these symptoms. Throughout the therapy, lymphocyte count and liver enzymes must be monitored regularly.

**In Type 2 diabetes mellitus** 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 levels .These drugs act by different mechanisms-

1. By increasing the secretion of insulin , hence, also called **insulin secretagogues** like **Sulfonylureas** ( Glipizide, Glyburide, Glimepride), **Meglitinides** ( Repaglinide, Nateglinide)- these act on sulfonylurea receptors present on the beta cells of pancreas and stimulate the release of insulin . ( K ATP channel blockers )
2. By increasing peripheral utilization of glucose like **Biguanides** (Metformin) and **Thiazolidinediones** ( Pioglitazone, Rosiglitazone) - **insulin sensitisers**- they increase the sensitivity of target tissues to insulin and decrease gluconeogenesis. Biguanides act as AMP K( AMP activated protein kinase ) activators while Thiazolidinediones act as PPAR gamma activators.
3. By decreasing the absorption of glucose from the gut- like alpha glucosidase inhibitors ( Acarbose, Voglibose, Miglitol ) - these drugs also increase the hydrolysis of disaccharides. [12-15]
4. **Incretin mimetics** -Incretins like Glucagon like peptides (GLP-1) are 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 and is rapidly inactivated by the enzyme DPP 4.( dipeptidyl peptidase 4) . GLP-1 plays an important role in blood glucose regulation as it enhances insulin secretion but can’t be given orally because it is rapidly destroyed by DPP4 enzyme.

In type 2 diabetes, production of incretins decreases and their rate of inactivation enhances such that 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 cleaving its substrate, are needed. These are **GLP-1 receptor agonists** and **DPP4 inhibitors** respectively.

They regulate blood glucose levels by the following mechanisms-

1. Enhance secretion of insulin
2. Decrease glucagon secretion
3. Delay gastric emptying (Slowing the rate at which food leaves the stomach ) and
4. Decrease appetite (Feeling less hungry , having a sense of fullness) .[16]

Both GLP1 receptor agonists and DPP4 inhibitors can increase the survival of beta cells due reduced apoptosis. This poses a potential risk of cancer.

**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 nausea, diarrhoea and constipation .These can be minimized by starting with low dose and increasing the dosage gradually.

Also, Semaglutide and Liraglutide, lower the risk of serious cardiovascular problems, such as heart attack and stroke, in people with obesity and diabetes.

**Tirzepatide** – is a novel drug useful in type 2 diabetes mellitus, when inspite 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 regulate blood glucose which leads to improved blood glucose control. Adverse effects of Tirzepatide are nausea ,vomiting ,diarrhea ,decreased appetite ,constipation, abdominal discomfort and abdominal pain .

Thydroid C cell tumors have been reported in rats.Tirzepatide should not be used in patients with family history of medullary thyroid carcinoma.

**DPP4 inhibitors-** dipeptidyl peptidase 4 inhibitors-

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 postprandial insulin release, decrease glucagon secretion, delay gastric emptying and suppress appetite They have longer plasma half life, used along eith sulfonylureas or metformin in resistant type 2 DM.

Side effects- Nasopharyngitis, GIT upset, diarrhoea,

Initially developed to treat type 2 diabetes **Incretin mimetics** can lead to loss of as much as 20% body weight which is much more than the anti-obesity drugs. They also improve blood pressure and cholesterol levels.

Another promising group of drugs for treatment of type 2 diabetes mellitus are the [sodium-glucose co-transporter-2 inhibitors](https://link.springer.com/article/10.1007/s13300-014-0089-4)  **SGLT-2 Inhibitors** .[20] SGLT 2 is present in the proximal tubule and is responsible for reabsorption of all the glucose in the proximal tubule. 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 - urinary tract infections, genital fungal infections, constipation, flu-like symptoms, dehydration , low blood pressure that can result in dizziness and fainting , impaired kidney function.

[Hypoglycemia](https://www.healthcentral.com/condition/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 popular in combination regimens with metformin and DPP4 inhibitors and combinations of all three and thiazolidinediones.

Miscellaneous drugs

**Amylin analogs** –

**Pramlintide** which decreases the secretion of glucagon ,delays gastric emptying and decreases appetite can also be 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.

**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]

**Ranolazine** , an antianginal drug , decreases glycosylated hemoglobin in experimental models.

**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. Epalrestst is an aldose reductase inhibitor . It delays accumulation of sorbitol. useful in diabetic neuropathy. Side effects are nausea , vomiting and liver dysfunction.

**Sevelamer** -It is primarily a phosphate binder with **Bile acid sequestrant** properties . It also decreases the levels of HBA 1C cholesterol and triglycerides . It increases the delivery of bile acids to the distal colon via its bile acid sequestering capability thereby promoting the release of GLP-1

**Sotagliflozin**

Dual SGLT1 /2 inhibitor . SGLT 1 is present in the gut, SGLT1 and 2 are present in the kidneys. Therefore, Sotagliflozin decreases the absorption of glucose from the intestine as well as the kidneys.

**Retatrutide-**

targets three hormones – GLP-1 and GIP similar to Tirzepatide and in addition glucagon .

**Glimins – Imeglimin**- improve overall functioning of the mitochondria present in the pancreas , liver and muscles for better control of blood glucose levels.

**Bromocriptine-** is a drug used for the treatment of Parkinsonism

**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 increasing the sensitivity of target tissues to insulin.

**Receptors**

1. GPR119, Glucose-dependent insulinotropic receptor (G-Protein coupled receptor 119)- is expressed in pancreatic β-cells and enteroendocrine cells , and stimulates insulin and incretin secretion.
2. Glucagon receptor antagonists.
3. Leptin analogues
4. Adiponectin receptor agonists
5. Analogues of fibroblast growth factor-21
6. GIPR, Gastric Inhibitory Polypeptide Receptor
7. AMPK, 5′-AMP-activated protein kinase.
8. Thyroid hormone receptors (THR) have typically been targeted in the treatment of metabolic disorders. THR are present in the liver, skeletal muscles, and kidneys in large numbers and have been shown to increase insulin sensitivity, and lower glucose levels in experimental models.

**Enzymes-**

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

Overall, Sulfonylureas, meglitinides and thiazolidinediones (TZDs) are most cost effective drugs . Sulfonylureas and meglitinides carry risk of hypoglycaemia and weight gain whereas Thiazolidinediones cause weight gain, oedema, heart failure and bone fractures. DPP4- and SGLT2 inhibitors are highly effective but their cost is a major deterrent.

In India, metformin is the most preferred first-line drug , with the DPP4 inhibitors catching up with SUs as second-line treatment after metformin while SGLT2 inhibitors are being used as third- or fourth-line antidiabetic drugs .

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